IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

PURDUE PHARMA PRODUCTS L.P., NAPP PHARMACEUTICAL GROUP LTD., BIOVAIL LABORATORIES INTERNATIONAL SRL, and ORTHO-MCNEIL, INC.,	)	
Plaintiffs,	)	C.A. No. 07-255-JJF
v.	)	
PAR PHARMACEUTICAL, INC. and PAR PHARMACEUTICAL COMPANIES, INC.,	)	**PUBLIC VERSION**
Defendants.	)	

DECLARATION OF STEFAN GROND, MD, DEAA IN SUPPORT OF DEFENDANTS' REPLY CLAIM CONSTRUCTION BRIEF

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Dated: August 22, 2008

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

PURDUE PHARMA PRODUCTS L.P., NAPP PHARMACEUTICAL GROUP LTD., BIOVAIL LABORATORIES INTERNATIONAL SRL, and ORTHO-MCNEIL, INC.,	:	
Plaintiffs,	:	C.A. No. 07-255-JJF (CONSOLIDATED)
v.	:	
PAR PHARMACEUTICAL, INC. and PAR PHARMACEUTICAL COMPANIES, INC.,	:	
Defendants.	:	

DECLARATION OF STEFAN GROND, MD, DEAA IN SUPPORT OF DEFENDANTS' REPLY CLAIM CONSTRUCTION BRIEF

I. BACKGROUND

1. I have been retained by counsel to Defendants Par Pharmaceutical, Inc. and Par Pharmaceutical Companies, Inc. ("Par") as a clinical expert relating to pain management and, in particular, the drug tramadol.

2. My curriculum vitae summarizes my educational and professional background, and includes a list of authored publications and lectures given. (**Exhibit A**).

3 I am Chief Physician of the Department of Anesthesiology and Intensive Care at the Hospital Lippe in Detmold, Germany, a teaching hospital of the Medical University of Hannover, Germany. From 2001 to 2007, I was an active full Professor at the Martin-Luther-University in Halle, Germany, a title I retained when I moved to Detmold.

4. I obtained my medical degree from the University of Cologne, Germany in 1985, and my Diploma in Anesthesiology and Intensive Care of the European Academy of Anesthesiology (DEAA) in 1992. I completed a residency in Anesthesia and Intensive Care at the University of Cologne. I am Board Certified in Germany in Pain Management, Anesthesiology, Intensive Care, Medical Quality Management and Emergency Medicine.

5. I have been prescribing tramadol since 1985 and have been clinically analyzing tramadol since 1987.

6. While working in the Sachsen-Anhalt state of Germany, I was Chairman of the Board of Pain Treatment of the Committee of Physicians from 2003 to 2007. In this capacity, I was responsible for overseeing the Board certification and training programs of physicians specializing in pain management.

7. Since 2007, I have been a Member of the Board of Narcotic Drugs of the German equivalent of the U S. Food & Drug Administration. Since 2005, I have been a Member of the Pharmaceutical Committee of the German Federal Commission of Physicians. In this capacity, I have been involved in establishing federal guidelines for the treatment of patients with cancer pain.

8. I have been a clinical investigator in more than 15 clinical studies, ranging from phase II to phase IV. These clinical studies primarily evaluated the use of opioids for pain management Of these clinical studies, two were focused on the drug tramadol.

9. I also conducted basic science research on opioid receptors at the Department of Anesthesia at the University of California, San Francisco from 1999 to 2000

10 I have authored approximately 89 original articles, 51 review articles, 28 book chapters and two books. The drug tramadol was the focus of approximately 6 of the original articles and approximately two of the review articles. In addition, tramadol was a subject of several other publications. One of my publications in which tramadol was studied was a key study that validated the guidelines established by the World Health Organization for the relief of cancer pain.

II. OPINION ON MEANING OF TERMS

11. I have been asked by Par's counsel to address the meaning of the claim terms "therapeutic effect;" "therapeutic effect for about 24 hours after oral administration;" and "therapeutic effect for at least about 24 hours" in United States Patent Nos. 6,254,887 ("the '887 patent") and 7,074,430 ("the '430 patent").

12. The claimed terms "therapeutic effect," "therapeutic effect for about 24 hours after oral administration," and "therapeutic effect for at least about 24 hours" are directed to the art of the clinical treatment of pain. One of ordinary skill in the art of the clinical treatment of pain in the 1993-1994 time frame[1] is generally an individual with a medical degree and a completed residency in a field that treats pain, such as anesthesiology, neurology, oncology, orthopedics and surgery.

13. In the 1993-1994 time frame, such a person of ordinary skill would have understood (and today would still understand) the claim terms "therapeutic effect," "therapeutic effect for about 24 hours after oral administration," and "therapeutic effect for at least about 24

[1] I was told that Par contends that the claims in suit are not entitled to a May 10, 1993 priority date. Accordingly, I refer to the relevant period generally as the 1993-1994 time frame and for the purposes of my opinion do not believe that what a person of ordinary skill would understand would be different in 1993 and 1994.

hours" to mean that analgesic efficacy was shown to exist in human patients suffering from pain in scientifically valid studies that take into account the placebo effect.

14. In the 1993-1994 time frame, the person of ordinary skill would have understood (and today would still understand) the term "therapeutic" to imply treatment of a patient suffering from a clinical condition, such as pain. The "therapeutic effect" of tramadol is analgesia in patients suffering from pain. Therefore, it can only be determined in patients experiencing pain and not in volunteers or subjects who are either pain-free or experience induced pain.

15. Pain is a complex and subjective experience that is caused by different physical, psychological and social mechanisms that affect the patient.

16. Typical physical causes of pain, and the mechanisms by which they act, are diverse. Pain may be caused by stimulation of pain receptors in soft tissue, bones or viscera, or by irritation of nerves. Pain in cancer patients may be caused by cancer growth, cancer treatment (e.g., surgery, radiation or chemotherapy) or other causes independent of the cancer. Post-operative pain may be caused by damage of nerves, muscle or bones; inflammation; or ischemia. There are many other examples demonstrating that pain in patients has different and multiple causes.

17. Psychological factors may have a major influence on the pain experience. For example, emotional states, depression, stress and anxiety may modulate the suffering of patients. Similarly, social factors, such as employment, family and finances may also be important for the pain experience. Furthermore, the pain experience has great influence on many psychosocial factors that over the course of time themselves contribute to the level and quantification of pain.

The relationship between these factors and the pain experience represents a dynamic feedback loop that may influence a patient's quality of life.

18. The psychosocial factors faced by a healthy volunteer who joins a drug study to be paid can be expected to differ substantially from those faced by a patient who suffers from a medical condition (e.g., cancer, trauma, post-operative condition, osteoarthritis, low back pain) that the patient comes to associate with pain. This would have been understood in the 1993-1994 time frame (just as it still is today).

19 Another difference between healthy volunteers and pain patients that may influence evaluation of therapeutic efficacy is the extent to which tolerance develops. For healthy volunteers subjected to induced pain, tolerance to the drug administered (requiring ever increasing dosages to obtain the same analgesic effect) is expected to be greater than for pain patients. This would have been understood in the 1993-1994 time frame (just as it is today).

20. Given these complex factors, one of ordinary skill in the 1993-1994 time frame would have understood that a claim of a "therapeutic effect" for tramadol would have been shown in human patients suffering from pain.

21. While *in vivo* testing in human subjects not suffering from pain may be appropriate to evaluate some parameters, such as bioavailability or absorption, they are inappropriate to evaluate the "therapeutic effect" of certain drugs, such as tramadol.

22. Even induced pain in healthy volunteers does not reflect the complex situation of pain patients. Therefore, the demonstration of an antinociceptive effect (i.e., a reduction in sensitivity to pain stimuli) in healthy volunteers cannot prove a "therapeutic effect."

23. In addition, a person of ordinary skill in the 1993-1994 time frame would have understood (and today would understand) a "therapeutic effect" of tramadol to be shown by a scientifically valid study. First and foremost, this requires the use of an appropriate control that takes into account the substantial placebo effect that would have been known by a person of ordinary skill at that time. Turner, J.A. et al. (1994) "The Importance of Placebo Effects in Pain Treatment and Research," JAMA 271(20): 1609-1614) ("Turner (1994)") (**Exhibit B**); Wall, P.D. (1993) "Pain and the placebo response," Ciba Foundation Symposium 174:187-211 ("Wall (1993)") (**Exhibit C**).

24. A placebo effect is an effect caused only by a patient's belief that, for example, the drug being studied is effective but not by the actual pharmacological effect of the drug. The placebo effect varies greatly and would have been understood to be greater than one-third (i.e., greater than one-third of patients treated with a placebo would feel analgesia) in the early 1990's. (Turner (1994) and Wall (1993)).

25 Furthermore, the demonstration of the therapeutic effect of a drug such as tramadol requires the measurement of pain by the patient. Unlike other physiological parameters, such as blood pressure, that may be measured objectively by a physician, pain is a subjective experience that can only be measured by the patient. At this time period, there were several widely-accepted methods used to evaluate pain. For example, self assessment of pain intensity using a verbal rating scale (VRS) or a visual analog scale (VAS). Each of these methods depends on the subjective evaluation by the patient of their pain experience, which again, is a multi-dimensional phenomenon in patients.

26 A person of ordinary skill at this time also would understand "therapeutic effect" to include not only an evaluation of a tramadol analgesic effect but also its side effect profile and influence on quality of life parameters that in turn affect the pain experience. Such factors may include whether the drug affects the patient's ability to sleep or to perform important activities such as walking, taking care of a household, washing oneself, getting out of bed, exercising and other activities that affect one's psychological state.

27. A person of ordinary skill at this time also would understand that a study to show the therapeutic effect of tramadol would need to include a sufficient number of patients to generate statistically significant results.

28. To demonstrate the therapeutic effect of tramadol for a specific period, a person of ordinary skill would have expected a study that measured pain scores at regular intervals during that specific period. For example, a study to evaluate therapeutic efficacy for 24 hours would necessarily include pain measurements at regular intervals, such as every four hours (i.e., at 0, 4, 8, 12, 16 and 24 hours).

III. OPINION THAT PHARMACOKINETIC DATA ARE NOT A BASIS TO SHOW THERAPEUTIC EFFECT

29 The '887 and '430 patents contain no pain studies of any kind and report only two limited pharmacokinetic studies (or blood levels, *in vivo* profiles or *in vivo* parameters) in healthy human volunteers. For multiple reasons, including the complex factors that cause pain in human patients, a study that measures only the levels of a drug in the blood of healthy human subjects is not an appropriate model to evaluate therapeutic effect. Given the complexities of tramadol metabolism, and its modes of action, a pharmacokinetic study is particularly inappropriate as a measure of tramadol's therapeutic effectiveness.

30. There is no established or useful correlation between serum concentrations of tramadol and its therapeutic effect that would allow one to extrapolate an expectation of a therapeutic effect (let alone a therapeutic effect for a specific time period) from blood levels. This was true in the 1993-1994 time frame and remains true today.

31. Several studies in postoperative pain have demonstrated a great inter- and intraindividual variability of plasma concentrations and could not fix narrow analgesic threshold concentrations. Grond, S and Sablotzski, A. (2004) "Clinical Pharmacology of Tramadol," Clinical Pharmacokinetics 43(13):879-923 ("Grond (2004)") (**Exhibit D**) at 892.

32 For tramadol, interpretation of the relationship between serum concentrations and therapeutic effect is especially difficult because of: (i) interactions among the two enantiomers of tramadol and its active metabolites; and (ii) a delay of effect resulting from transport from plasma to the central nervous system (Grond (2004) at 891).

33. Tramadol is administered as a racemic mixture of two enantiomers (commonly known as (+)-tramadol and (–)-tramadol) that are essentially metabolized by the liver, producing the (+)- and (-)-metabolites, respectively. As early as 1981, eleven metabolites of tramadol were known. Lintz W. et al. (1981) "Biotransformation of tramadol in man and animal [in German]," Arzneimittel Forschung 31(11):1932-1943. More recently, a total of 23 metabolites of tramadol were identified.

34. Tramadol's analgesic effect is caused by stimulation of the mu opioid receptors, by the inhibition of serotonin re-uptake pathways and by the inhibition of norepinephrine re-uptake pathways. In the 1993-1994 time frame, a person of ordinary skill would have understood that tramadol's analgesic effect was produced through multiple mechanisms of

action. Raffa, R.B. et al. (1992) "Opioid and nonopioid components independently contribute to the mechanism of action of tramadol, an 'atypical' opioid analgesic," J. Pharmacol. Exp. Ther. 260:275-285; Raffa, R.B. (1993) "Complementary and synergistic antinociceptive interaction between the enantiomers of tramadol," J. Pharmacol. Exp. Ther. 267:331-340.

35. One of the metabolites of tramadol—known as (+) O-desmethyl-tramadol or the (+)-M1 metabolite—has a much higher (approximately 700 times higher)[2] affinity for the mu opioid receptor than tramadol, and thus, is substantially responsible for the opioid effect of tramadol. (+)-Tramadol acts as an inhibitor of the serotonin re-uptake, while the (-)-tramadol acts as an inhibitor of norepinephrine re-uptake. And so it is well known that the analgesic effect achieved by tramadol is achieved by three different "drugs" acting by at least three distinct mechanisms (i.e., (+)-tramadol, (-)-tramadol and (+)-M1 metabolite).

36. A further reason why a measurement of the blood levels of the tramadol enantiomers in the blood is not a valid means to evaluate therapeutic effect is that the rate and extent of the metabolism of the active metabolite, (+)-M1, was known to vary widely based on the activity of liver enzyme cytochrome P450 in the patient. *See, e.g.*, Poulsen L., Arendt-Nielsen L., Brosen K., et al. (1996) "The Hypoalgesic Effect of Tramadol in Relation to CYP2D6," Clin. Pharmacol. Ther. 60(6):636-44.

37. The determination of a minimum effective concentration for the analgesic effect of tramadol is not possible because no quantitative data are available for the roles of tramadol or its enantiomers, (+)-M1 and other metabolites. (Grond (2004) at 892; Grond, S. et al. (1999)

[2] Gillen, C. et al. (2000) "Affinity, potency and efficacy of tramadol and its metabolites at the cloned human mu-opioid receptor," Naunyn Schmiedebers Arch Pharmacol. 362(2):116-121

"Serum concentrations of tramadol enantiomers during patient-controlled analgesia," Br. J. Clin. Pharmacol. 48:254-257 (**Exhibit E**) at 256).

38. A further complexity results from the site of action in the body. The site of action for the two tramadol enantiomers, as well as the (+)-M1 metabolite, is the central nervous system, which requires that those active substances transverse the blood-brain barrier. A measure of blood concentration is not the same as a measure of the concentration of any active substance at its site of action (i e., the central nervous system).

IV. OPINION THAT *IN VITRO* DISSOLUTION PROFILES ARE NOT A BASIS TO SHOW THERAPEUTIC EFFECT

39. *In vitro* dissolution profiles are even further removed from any evaluation of therapeutic effect than pharmacokinetic studies.

40. The reasons stated in paragraphs 29 to 38 as to why pharmacokinetic studies are not a basis to show a therapeutic effect apply equally to why *in vitro* dissolution profiles are no measure of a therapeutic effect.

41. Moreover, *in vitro* dissolution profiles are merely one parameter of potential absorption (a pharmacokinetic parameter) of an active substance. Absorption is further affected by a variety of other factors, such as the *in vivo* environment in the gastrointestinal system, food intake, alcohol intake, and bowel movements. Furthermore, pharmacokinetics are influenced by additional factors, such as hepatic metabolism and renal elimination.

I declare under penalty of perjury that the foregoing is true and correct.

Executed on: July 1, 2008

Stefan Gronli, MD, DFAA

IN THE UNITED STATES DISTRICT COURT
DISTRICT OF DELAWARE

CERTIFICATE OF SERVICE

I hereby certify that on August 22, 2008, I electronically filed the foregoing document with the Clerk of Court using CM/ECF which will send notification of such filing(s) and Hand Delivered to the following:

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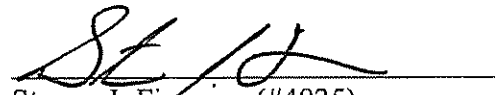

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EXHIBIT A

Curriculum Vitae

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Professor of Anesthesia
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2007 to present	Chief Physician of the Department of Anesthesiology and Intensive Care at the Hospital Lippe in Detmold, Germany, a teaching hospital of the Medical University of Hannover, Germany
2007 to present	Member of the Board of Narcotic Drugs of the Bundesinstitut für Arzneimittel and Medizinprodukte (the German equivalent of the U.S. FDA)
2005 to present	Member of the Pharmaceutical Committee of the German Federal Commission of Physicians
2001 to present	Professor of Anesthesia, Martin-Luther-University Halle-Wittenberg, Germany (teaching until 2007)
2003 – 2007	Chairman of the Ethics Committee, Martin-Luther-University Halle-Wittenberg, Germany
2003 – 2007	Chairman of the Board of Pain Treatment of the Commission of Physicians of Sachsen-Anhalt (State of Germany)
2001 – 2007	Director of Pain Clinic Vice-Chairman of the Department of Anesthesia and Intensive Care Chair of the Pain Fellowship Program Martin-Luther-University Halle-Wittenberg, Germany
1999 – 2000	Research Anesthetist, Department of Anesthesia University of California, San Francisco, USA
1996 – 2000	"Privatdozent" (equivalent to Assistant Professor) of Anesthesia and Intensive Care and Staff Anesthetist, Department of Anesthesia and Intensive Care University of Cologne, Germany
1990 - 1996	Staff Anesthetist, Department of Anesthesia and Intensive Care University of Cologne, Germany
1992	European Diploma in Anesthesiology (European Academy of Anesthesiology)
1985 – 1990	Resident, Department of Anesthesia and Intensive Care University of Cologne, Germany
1989	Doctorate
1985	State Medical Examination
1985	Graduation from Medical School University of Cologne, Germany

2007	Board Certification in Emergency Medicine
2004	Board Certification in Medical Quality Management
2001	Board Certification in Pain Management
1997	Board Certification in Intensive Care
1990	Board Certification in Anesthesiology

Since 1988, clinical investigator in more than 15 clinical studies phase II-IV.

Coordinating Investigator of 3 international multicenter studies.

Member of the International Association for the Study of Pain (IASP)
Member of the European Society of Anesthesiologists (ESA)
Examiner for the European Diploma in Anesthesiology and Intensive Care
Member of the German Society of Anesthesiology and Intensive Care
Delegate for the German Interdisciplinary Association for Pain Treatment (DIVS)
Member of the German Pain Society

Author of 89 original articles, 51 reviews, 28 book chapters and 2 books

Stefan Grond

Publications

1. Original Papers

*(Impact-Factor nach Journal Citation Reports 2003, * Senior author)*

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Opioids in chronic non-cancer pain: matrix technology of fentanyl transdermal patch
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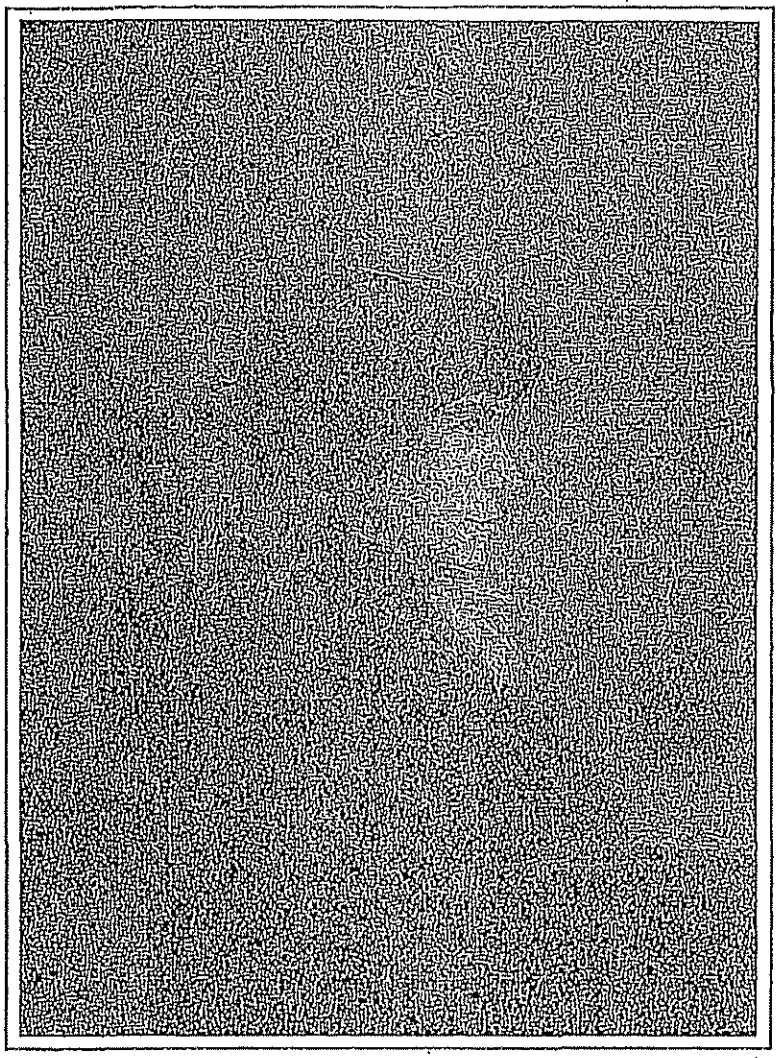
EXHIBIT B

JAMA

The Journal of the American Medical Association

May 25, 1994



Review

The Importance of Placebo Effects in Pain Treatment and Research

Judith A. Turner, PhD; Richard A. Deyo, MD, MPH; John D. Loeser, MD; Michael Von Korff, ScD; Wilbert E. Fordyce, PhD

Objective.—To estimate the importance and implications of placebo effects in pain treatment and research from the existing literature, with emphasis on their magnitude and duration, the conditions influencing them, and proposed explanations.

Data Sources.—English-language articles and books identified through MEDLINE (1980 through 1993) and PsycLIT (1967 through 1993) database searching, bibliography review, and expert consultation.

Study Selection.—Articles were included if they pertained to the review objectives.

Results.—Placebo response rates vary greatly and are frequently much higher than the often-cited one third. Placebos have time-effect curves, and peak, cumulative, and carryover effects similar to those of active medications. As with medication, surgery can produce substantial placebo effects, and this possibility is commonly overlooked in case series reports on back surgery. Individuals are not consistent in their placebo responses, and a placebo-responder personality has not been identified. Models advanced to explain placebo effects emphasize the role of anxiety, expectations, and learning.

Conclusions.—Placebo effects influence patient outcomes after any treatment, including surgery, that the clinician and patient believe is effective. Placebo effects plus disease natural history and regression to the mean can result in high rates of good outcomes, which may be misattributed to specific treatment effects. The true causes of improvements in pain after treatment remain unknown in the absence of independently evaluated randomized controlled trials.

(*JAMA*. 1994;271:1609-1614)

TWO questions are of major interest to clinicians and researchers with respect to pain treatments: What is the efficacy of a specific treatment (under what conditions and for what patients will it improve certain dimensions of outcome), and why do patients improve with it (what is the mechanism)? There are three general reasons for clinical improvement in a patient's condition.

1. Natural history and regression to the mean. Most acute and some chronic pain problems resolve on their own irrespective of treatment.[1] Many individuals have recurrent episodes of pain such as headache or low back pain, interspersed with no or minimal pain. Patients with chronic conditions typically have fluctuating symptoms and seek medical care (and enroll in research studies) when symptoms are at their worst. Thus, the next change is likely to be an improvement. This tendency of extreme symptoms or findings to return toward the individual's more typical state is known as regression to the mean.[2] Apparent improvement may also reflect measurement error or random variation in patient symptoms over time.[3]

2. Specific effects of treatment, attributable to the characteristic content of the intervention.

3. Nonspecific effects of treatment, attributable to factors other than specific active components. These include physician attention, interest, and concern in a healing setting; patient and physician expectations of treatment effects; the reputation, expense, and impressiveness of the treatment; and characteristics of the setting that influence patients to report improvement. The term *placebo effect* is often used synonymously with *nonspecific effects*.

It is helpful for clinicians to know the contributions of each of these processes to treatment effects in order to make optimal treatment decisions. It is also essential for investigators to understand the extent to which placebo effects can account for improvements observed in clinical studies. The purpose of this article is to review the literature on placebo effects, with an emphasis on their magnitude and duration, the conditions influencing them, proposed explanations, and their implications for pain treatment research. Although this article pertains to pain problems in general, low back pain is used frequently as a specific example because it is highly prevalent, costly, and a leading reason for seeking health care.

METHODS

To identify relevant English-language articles for this review, the MEDLINE

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bibliographic database (1980 through 1993) and the PsycLIT database (1967 through 1993) were searched using the term *placebo effect*. The MEDLINE search yielded 163 articles, and the PsycLIT search yielded 41 articles (nine of which were also found in MEDLINE). Additional articles and books were identified from personal files, bibliography reviews, and requests to professionals with expertise in the area. Three books and 75 articles were read for this review.

RESULTS

Definitions

A placebo is an intervention designed to simulate medical therapy, but not believed (by the investigator or clinician) to be a specific therapy for the target condition.[3] It is used either for its psychological effect or to eliminate observer bias in an experimental setting.[3] Alternatively, it could be a treatment now believed to be inefficacious, though believed efficacious at the time of use.[3] A placebo effect is a change in a patient's illness attributable to the symbolic import of a treatment rather than a specific pharmacologic or physiological property.[3] Thus, a placebo effect does not require a placebo. A placebo response refers to any change in patient behavior or condition following the administration of a placebo.[4] The literature does not always use these distinctions, and there are many misconceptions, including the following beliefs: (1) about one third of patients will have a placebo response in any clinical trial; (2) placebo effects are necessarily brief; (3) certain personality types are more likely to be placebo responders; (4) placebo responders had nothing wrong with them to begin with; and (5) giving a placebo is the same as doing nothing.

Placebo Effects of Medical Treatments

The widely accepted one-third placebo response rate is based on the classic article by Beecher.[5] This was a review of 15 studies of patients suffering a variety of conditions (postoperative pain, cough, angina pectoris, headache, drug-induced mood changes, seasickness, anxiety and tension, and common cold). On average, symptoms were "satisfactorily relieved" by the placebo in 35% of patients in these studies, but the placebo response rate ranged from 15% to 58%. Wide variation in placebo response rates has since been observed in other settings as well. The Table shows examples of response rates after sham treatments for painful conditions and in studies of treatments initially considered efficacious but later shown to be no better than placebo. The combined results for the treatments reviewed by Roberts et al[6] that were originally believed efficacious but later abandoned averaged 70% excellent or good outcomes, presumably reflecting placebo and natural history effects. Sham treatments can also produce excellent results. For example, 64% of patients who underwent a sham tooth-grinding procedure for myofascial pain dysfunction (temporomandibular disorder) reported total or near-total symptom remission.[9]

In sum, rates of good patient outcomes after treatments that have no specific therapeutic effects vary considerably across studies, but are strikingly high on average. Even patients with a long history of back pain show clinically and statistically significant improvement with placebo. Deyo et al[10,11] found that scores on measures of pain severity, pain frequency, and functional status improved, on average, 20% to 40% after patients with back pain received sham transcutaneous electrical nerve stimulation plus hot packs, despite the chronicity of their pain (average duration, 4 years).

Placebo Effects of Surgery

Beecher[12] emphasized that surgery could evoke a placebo effect and urged caution in interpreting the benefit of new operations. Similarly, Spiro[13][p42] wrote that "skeptics have long noted that an operation, particularly a new one, seems to bring benefit for several years until it is reevaluated and then often abandoned." He noted that new operations are often associated with a new diagnostic device yielding information that is interpreted as explaining a pain problem. Attempts are then made to correct the problem by operations or drugs. Spiro suggested that the experience of surgery and the symbol of the scar must themselves be important sources of pain relief.

In the 1950s, there were two double-blind randomized trials of internal mammary artery ligation vs skin incision (with vessel exposure but no ligation) for patients with angina pectoris.[7,8] At the time, internal mammary artery ligation was believed to help angina pectoris by increasing coronary artery blood flow through increased collateral circulation. As summarized in the Table, these studies demonstrated substantial and sustained improvement in angina after skin incision alone.

Placebo effects of back surgery are suggested by Spangfort's[14] review of long-term outcomes of 2504 diskectomies for lumbar disk disease. Complete relief of sciatica was noted in 37% and complete relief of back pain in 43% of patients who had no disk herniation (negative surgical exploration). There is no known therapeutic effect of surgical exploration of the lumbar spine; changes in patient status were most likely attributable to placebo effect and natural history.

The success rates after sham or discredited procedures may be compared to the success rates in spine surgery case series. Across 74 studies of surgery for lumbar spinal stenosis, an average of 64% of patients had good or excellent outcomes.[15] Similarly, 68% of patients had good or excellent results among 47 studies of lumbar spinal fusion.[16] These figures reflect outcomes reported at long-term follow-up; the absence of randomized controlled trials precludes the interpretation of the outcomes as resulting from specific surgery effects as opposed to placebo effects plus natural history. However, the figures are similar to the average 70% excellent or good outcomes for several abandoned medical and surgical therapies.[6]

In sum, nonspecific influences plus natural history and regression to the mean play an important role in pain relief after surgery. Important nonspecific influences likely include subjects' and surgeons' expectations of improvement. This situation with respect to low back surgery is highlighted further by the weak association between imaging test results and symptoms,[1,17-22] and between technical success of surgery (eg, solid fusion) and symptom improvement.[22,23]

Pharmacokinetics of Placebo Response

Placebos have demonstrable time-effect curves and peak, cumulative (greater effects with repeated administrations), and carryover effects after cessation of treatment, which mimic those of active medications.[24] When varying doses of analgesic followed by a placebo are administered, patients' placebo responses correspond in degree of pain relief over time to their original dosage of analgesic.[25] Dose-response effects have also been demonstrated; for example, two placebo capsules were shown to have more pronounced effects than one.[25]

Placebos are associated with side effects, especially drowsiness, headaches, nervousness, insomnia, nausea, and constipation.[27] Perceptual characteristics of drug preparations play a role in individuals' responses. Larger capsules tend to be viewed as stronger, yellow capsules tend to be perceived as stimulants or antidepressants, and white capsules tend to be perceived as analgesics or narcotics.[28] Injections may produce larger effects than do pills.[29]

The duration of response to placebos has not been studied extensively. Patients with painful diabetic neuropathy who re-

Placebo Effects in Studies of Medical and Surgical Treatments for Painful Conditions

Source	Condition	Treatment(s)	% Improved	Comments
Roberts et al[4] (review of treatments originally believed efficacious but later found to be ineffective)	Herpes simplex virus infections	Levamisole*	85% excellent or good	Average across uncontrolled trials that asserted the efficacy of levamisole
		Photodynamic inactivation treatment*	85%-100% excellent or good	Average across 5 uncontrolled trials
		Topical application of organic solvents*	83% excellent or good	Average across 5 uncontrolled trials
	Duodenal ulcers	Gastric freezing*	98%-100% marked or complete relief 65% good/excellent	Results in initial studies Average across 8 studies that asserted the efficacy of gastric freezing
Cobb et al[7]	Angina pectoris	Internal mammary artery ligation	83% significant improvement, 34% decrease in nitroglycerine use	During first 6 mo after surgery
		Skin incision only	56% significant improvement, 42% decrease in nitroglycerine use	
Dimond et al[8]	Angina pectoris	Internal mammary artery ligation	After surgery, 100% improved	During year after surgery, 69% reported over 50% improvement in angina
		Skin incision only	After surgery, 100% improved in exercise tolerance, nitroglycerine use, and angina	During year after surgery, 100% reported over 50% improvement in angina
Goodman et al[9]	Myofascial pain dysfunction (temporomandibular disorder)	Sham tooth-grinding	64% total or near-total symptom remission	

*Treatment subsequently found to be no better than placebo in controlled trials.

ceived a placebo reported a decrease in pain intensity for the first 3 weeks, followed by a partial return toward baseline levels during the next 3 weeks.[29] Clinically significant improvement in angina symptoms was maintained as long as 1 year after sham surgery.[8] These studies do not allow for a separation of placebo from natural history effects.

Nocebo Effects

Nonspecific influences of treatments may produce adverse effects, sometimes referred to as "nocebo effects." The overall incidence of adverse events in healthy volunteers during placebo administration was 19% in a review of 109 double-blind drug trials.[30] Placebos can also make preexisting symptoms worse. For example, in a double-blind study[31] of a magnetic device for which pain-relieving qualities were claimed, 13 of 58 pain patient subjects discontinued treatment after one or two treatments because their pain was worse. Six months later, three of these patients believed the treatment made their pain permanently worse. Placebos can also produce pain in normal subjects. Headaches were reported by 70% of students told that a (nonexistent) electric current was passing through their heads.[32]

Very little research has focused on negative nonspecific influences in medicine. One general practitioner randomly assigned his patients who had symptoms but no abnormal signs and in whom no definite diagnosis could be made to a positive or a negative encounter with him.[33] In the positive encounter, patients were given a diagnosis and told they would be better in a few days. In the negative encounter, the doctor told patients he was not certain what was the matter with them. Two weeks later, 64% of the positive group, but only 39% of the negative group, reported that they had gotten better (P=.001). The author speculated that these minor illnesses would be expected to resolve spontaneously by 2 weeks in the majority of patients, and that the 61% nonimprovement rate in the negative encounter group reflected adverse effects of the encounter.

FACTORS INFLUENCING PLACEBO RESPONSES

Patient Factors

Efforts to identify personality, demographic, and other characteristics that predict placebo responses have had little success.[34] In fact, individuals tend not to be consistent about showing placebo responses across placebo administrations.[35,36] However, patient expectations of treatment effects clearly influence their responses. For example, when subjects were given a pill containing only a magnet to measure stomach contractions, the contractions increased, decreased, or did not change according to the effects they were told the pill would cause.[37] In asthmatic patients, isotonic saline produced increases or decreases in airway resistance according to what patients were told to expect.[38] Further, when patients were given a true bronchodilator, its effects were about twice as great if patients were told it would produce this effect than if they were told it would produce the opposite effect. The patient's positive attitude toward the provider and toward the treatment have been shown to predict improvement in studies of psychiatric outpatients treated with placebo, psychotropic drugs, or psychotherapy.[34] There is also some evidence that highly anxious subjects show the greatest placebo responses.[34]

Highly compliant patients may have better outcomes than noncompliant patients, even when complying with a placebo. In a randomized trial to evaluate the efficacy of lipid-lowering drugs in the therapy of coronary heart disease, patients in the placebo arm were divided between those who were highly compliant (took at least 80% of placebo capsules) and those who were less compliant (took less than 80% of capsules).[39] Even after controlling for 40 known or suspected coronary risk factors, the placebo noncompliers had a 5-year mortality rate 57% higher than that of the compliers. We may hypothesize that placebo effects had some effect on mortality, or that patient compliance related to other characteristics associated with mortality, but not assessed in the study.

Provider Factors

The provider's warmth, friendliness, interest, sympathy, empathy, prestige, and positive attitude toward the patient and toward the treatment are associated with positive effects of placebos as well as of active treatments.[34] The importance of provider expectations was illustrated in a study of a new antihypertensive drug.[40] In the middle of this double-blind study, partners of the enthusiastic physician administering the drug broke the code. Without telling him which pills were the placebo and which were the drug, they told him that the drug, though effective, appeared similar to existing

drugs. Although less enthusiastic, they decided to complete the study. The difference between the drug and placebo was maintained, but there was an immediate and marked increase in the blood pressures of both groups.

In a double-blind study of dental extractions,[41] placebo responses were compared for patients in two groups: those whose clinicians knew they would administer a narcotic analgesic, a placebo, or a narcotic antagonist vs those whose clinicians knew they would administer only a placebo or narcotic antagonist. Placebo patients in the first group had significantly less pain. Because the two placebo groups differed only in the clinicians' knowledge of the range of possible treatments, this knowledge seems to have resulted in subtle behaviors that influenced patient responses.

EXPLANATIONS FOR PLACEBO EFFECTS

Decreased Anxiety

Stress and anxiety adversely affect several physiological processes and increase symptom reporting. Placebos seem to be most effective for highly anxious subjects, and placebo effects are often attributed to anxiety reduction and associated decreased suffering.[42] Placebos have been shown to decrease anticipatory anxiety.[43] However, it is not clear whether anxiety reduction is a cause of the placebo effect, or a component of it.[44]

Expectations

There are several possible explanations for how subject and researcher or clinician expectancies influence placebo effects. A patient's expectation that treatment will relieve symptoms may reduce anxiety and thus ameliorate symptoms. Expectancy of improvement may result in the patient's viewing the pain problem more positively and as more controllable. Thus, patients may be more likely to notice small improvements, to disregard negative events, and to interpret ambiguous stimuli favorably.[45] Changes in appraisals and expectancies may lead to beneficial behavior changes. For example, a low back pain patient may resume physical and functional activities he or she had avoided because of fear of pain or harm.

Learning

Treatment may have a positive effect because of its association with effective treatments the patient has had before (this learning process is referred to as conditioning). Thus, inert or neutral drugs, procedures, people, and places can come to function as conditioned stimuli or discriminative stimuli for the alleviation of symptoms, if they have been associated repeatedly with powerful unconditioned stimuli (eg, penicillin, nitroglycerine, analgesics) that reliably relieve symptoms.[46] Further, neutral stimuli (eg, the physician, the physical examination, and medication prescription) associated with the reduction of unpleasant symptoms may acquire positive conditioned properties for healing and anxiety reduction.

Experiments have demonstrated that placebo responses can be conditioned.[47] Furthermore, the direct experience of conditioning appears to be more powerful than expectancy formed through verbal persuasion.[48] Past treatment responses may influence a patient's responses to subsequent treatments in a positive or negative manner, depending on the prior history. This raises one possible explanation of why repeated back surgery yields progressively poorer results and sometimes makes patients worse rather than better.[49]

Endorphin Effects

It has been suggested that placebo responses may be mediated by endogenous opiate release in the central nervous system.[50] However, subsequent studies have yielded contradictory results, and the role of endogenous opiate processes is unclear at present.[42,51,52]

Conclusions

These models are not mutually exclusive, and each of these factors may play a role in placebo effects. In fact, Roberts[53] has argued persuasively for dropping the term *placebo* altogether. The understanding of placebo effects may be advanced by studies undertaken to examine the variety of potential influences other than specific treatment effects on patient outcomes, including natural history, regression to the mean, patient expectations, provider expectations, characteristics of the treatment situation that influence patients and physicians to behave in certain ways (eg, to report improvement), conditioning, and psychophysiological states such as anxiety and relaxation.[53]

IMPLICATIONS FOR RESEARCH DESIGN

Placebo effects are found with drugs, medical treatments, surgery, biofeedback, psychotherapy, and even diagnostic tests.[40,54] Thus, placebo effects can play a role in all interactions between provider and patient. Only independently evaluated (ie, not by the treating clinicians, and preferably by observers unaware of the treatment assignment) randomized controlled trials can establish an effect of a treatment above and beyond natural history of the condition and nonspecific effects. Random assignment of patients to treatment and control conditions is essential to reduce systematic bias in group membership, which may lead to differential improvement attributable to differences in patient characteristics rather than in the treatment. However, even in randomized controlled trials, physician and patient know there is a sham treatment and a real treatment, and outcomes are influenced by their expectancies and beliefs about which treatment the patient received. If either or both can guess (eg, by side effects) which treatment the patient received, or if one treatment is more credible, this may bias the study results. To the extent that the patient or clinician believes a treatment may be ineffective, the power of nonspecific effects will be reduced or underestimated.

Therefore, the control treatment in a trial should be as similar as possible to the active treatment, to create similar expectations. Patients receiving sham therapy should have visit frequency, contact, and support equivalent to that in the active therapy condition. It can be difficult to create placebo controls that appear to be active treatments, but creative placebos have been devised (eg, sham transcutaneous electrical nerve stimulation, the use of misplaced needling as a control for acupuncture, the use of subtherapeutic weight as a control for traction, and the use of massage as a control for spinal manipulation). Trials in which control treatments mimic the active intervention typically have found less advantage of the active treatment over the control than have trials with obviously different types of therapy or with inert placebo controls.[55,56]

A completely untreated group (eg, waiting list) is not the same as a placebo-treated group. A waiting list condition controls for the effects of the passage of time, but not for patient expectations. However, an untreated group condition in addition to a placebo group can help distinguish nonspecific effects from natural history. For chronic conditions, long baselines with multiple measures of the outcome variable before treatment can reveal changes in the absence of treatment and thereby help to estimate the magnitude of regression to the mean as a source of within-patient change.[57,58]

Ethical and practical factors make it difficult to conduct surgery trials with sham controls. For situations in which it is not possible to have a sham surgery control condition, randomized trials of surgery vs credible alternative nonsurgical therapies may be feasible, as has been done with coronary artery bypass surgery[59] and diskectomy.[60]

IMPLICATIONS FOR CLINICIANS

The administration of any treatment, including surgery, has physiological and psychological effects on the patient, and these are interrelated. There are placebo effects whenever the patient and the clinician perceive the treatment as effective. These effects can be potent and can lead to erroneous claims of efficacy for any type of treatment. These effects are likely to be strongest when the patient is anxious, the physician is perceived as having great expertise, the patient and physician believe the treatment is powerful, and the treatment is impressive and expensive. Placebo effects act synergistically with active treatment effects and natural history to influence patient outcomes. Physicians should use these nonspecific effects to their (and their patients') advantage. However, it is a gross error to use a placebo to assess whether a patient's pain or disease is "real," and to dismiss or delegitimize the complaint on the basis of a placebo response.

Physicians who use inactive treatments in the hopes of producing positive placebo effects run several risks. Patients may feel deceived if they discover they have been treated with a placebo. The placebo can produce adverse reactions. Failure to improve as expected may cause the patient to view his or her problem as more serious, and the patient may consequently become more concerned about it.[45] Failure to improve may also increase the risk of not improving with subsequent treatments.

Some patients with chronic pain may fail to respond to a treatment that is effective for other patients. This may be especially likely, due to previous learning experiences, if the patient previously responded poorly to different treatments, including those that were, unknown to the physician, no more than placebos. These patients may also be influenced by psychosocial, economic, and other factors that cause them to continue to fail additional treatments.

CONCLUSIONS

In most pain treatment and research situations, nonspecific effects of treatment are underestimated, and patient improvement is likely regardless of treatment. Nonspecific effects, natural history, and regression to the mean must be distinguished from specific effects when medical and surgical treatments are evaluated. It cannot be assumed that a treatment whose response rate is more than one third is better than placebo. The extent to which patient outcomes after a medical or surgical treatment reflect nonspecific effects, regression to the mean, natural history, or specific treatment effects is unclear in the absence of randomized controlled trials with outcomes assessed by persons blind to the patient's treatment. Our reviews[15,16,61] of the published literature on the treatment of low back pain have repeatedly found that few, if any, of the articles suggest that outcomes could be attributable to natural history or nonspecific effects. These effects are likely to be substantial, may be sustained over long periods of time, and may explain some or all of the benefits attributed to treatment. There are important implications for research and clinical training in all areas of medicine. The quality of the interaction between the physician and patient can be extremely influential in patient outcomes, and, in some (perhaps many) cases, patient and provider expectations and interactions may be more important than specific treatments.

Analysis and interpretation of placebo-related findings brings us to consider the nature of illness and disease and the relationships between body processes and the environment. Confusion and uncertainty among physicians and other health care professionals about placebo effects suggest an inadequate appreciation of the interaction of body processes with past experience, anticipated events, and immediate environmental influences. Further, the body's capacity to modulate symptoms and suffering involves more than simply "psychological factors," where those are seen as traits or personality characteristics. Symptoms, illness, and their changes over time reflect complex interactions between anatomical and neurophysiological processes, on the one hand, and cognitive-behavioral and environmental factors on the other. The findings reviewed herein support the thesis that these factors are inextricably intertwined.

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Pain and the placebo response

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Abstract. The placebo response is a powerful widespread phenomenon which relieves many conditions including pain. It depends on the patient's belief or expectation that the therapy is effective. It is an unpopular topic because it is confused with quackery or seen as an expensive artifact or taken to challenge the rationale of a therapy or to mock the reality of the senses. In order to avoid taking the subject seriously, myths are invented claiming that placebos work only on hysterics or hallucinators or that they are the equivalent of doing nothing or that they act only on the mental results of pain and not on the pain itself. These myths are dismissed. A model of the brain is presented in which preconscious decisions are made as to appropriate behaviour. Pain is perceived only after a decision has been made that it is appropriate to the biological needs of the individual.

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The word placebo has been used since the 18th century as a term for mock medicine. Its origin and meaning are usually given as a simple translation from the Latin as 'I will please'. I find that a highly improbable use of Latin by educated men of the time who would actually have said 'Placebit', 'It will please'. It seems to me much more likely that the word alludes to Psalm 116:9 'Placebo Domino in regione vivorum', which appears in the King James Bible as 'I will walk before the Lord in the land of the living'. This line beginning with Placebo is the first line of the vespers for the dead. Priests and friars pestered the populace for money to sing vespers for the dead. Placebo could have been the derisory word for these unpopular and expensive prayers, just as the words hocus pocus come from the first line of the Communion, 'Hoc est corpus', 'This is the body (of Christ)'. This is surely the way in which Geoffrey Chaucer (1340) used the word placebo when he writes, 'Flatterers are the devil's chatterlaines for ever singing placebo', as does Francis Bacon (1625) 'Instead of giving Free Counsell sing him song of placebo'. This adds a more subtle meaning to the word where the sycophant tells the listener what he expects and wants to hear, rather than the truth. That remains a placebo.

This topic needs no excuse because it is full of surprise, power and paradox. However, there are three reasons why it is relevant to introduce the facts of the

phenomenon to philosophers as well as to brain scientists. First, one notices a tendency for philosophers to use pain as a basic starting point for consideration of sensation and perception, because they think it can be presented as a simple phenomenon with obvious cause and inevitable effect and with a neural mechanism linking the two with confidence. The placebo should disenchant them of that and substitute intrigue. Second, theory is often challenged by experimenters with examples of subtle tricks played on conscious experience by our inability to cope with threshold ambiguous situations. Too often, neurological cases presented as educational material are so rare that I have never seen such a case or, if I have, I have a quite different interpretation from the experts. The placebo response is very common and rugged and operates in the presence of massive causes and effects. Finally, I wish to propose experiments which may emerge as much from philosophical clarity as from the testing of traditional hypotheses.

I will not attempt a precise definition of the placebo or of its effect. Those who require them can wade their way through the first 163 turgid pages of an otherwise lively book edited by White et al (1985). The reason for this agonized search for an acceptable definition is that most definitions threaten to breach the general obsession with a clear separation of mental from bodily sites of action. This search goes beyond the pleasures of academic, pedantic, talmudic need for acceptable precision. Legal regulations governing the introduction of a new pharmaceutical compound require the company to demonstrate that the novel molecule has a specific therapeutic action which is more powerful than the company's and doctor's and patient's belief that the novel molecule has a specific therapeutic action. A satisfactory answer is worth millions of pounds. It takes the question out of the philosophers' conundrum-riddled tutorial onto the floor of the stock exchange. It demands a precise dissection of the 'true' truth from the generally accepted, even universally accepted, 'believed' truth. Whatever the definition, it has nothing to do with the existence of a rationale for the statement. The question applies equally to the herbalist who states, 'The experience of the ages allows me to assure you that infusion of foxgloves helps dropsy', as to the pharmaceutical company which states, 'MK-801 helps strokes because excitotoxic amine-elicited calcium ion entry depends on NMDA channels which are antagonized by MK-801'. For what follows, I need go no further than Burton in 1628 in *The Anatomy of Melancholy*, 'There is no virtue in some (folk remedies) but a strong conceit and opinion alone which forceth a motion of the humours, spirits and blood which takes away the cause of the malady from the parts affected' and 'An empiric oftentimes, or a silly chirugeon, doth more strange cures than a rational physician because the patient puts more confidence in him.'

Two examples of the placebo effect

I wish here to give only two contemporary examples of the effect of strong opinions from the legion of placebo effects. Surgery is rarely the subject of a

placebo test, in spite of an admonition by Finneson (1969) in his book on surgery for pain: 'Surgery has the most potent placebo effect that can be exercised in medicine'. In the 1950s, it became a common practice to ligate the internal mammary arteries as a treatment for angina pectoris. Angina is a painful condition attributed to an inadequate blood supply of muscle in the heart wall. The rationale for the operation was that if the internal mammary arteries were ligated, the blood in these arteries would find alternative routes by sprouting new channels through nearby heart muscle, thereby improving the circulation in the heart. This relatively simple operation was carried out in large numbers of patients to the satisfaction of many. However, the rationale came under suspicion when pathologists were unable to detect any of the supposed new blood vessels in the heart. Therefore, two groups of surgeons and cardiologists (Cobb et al 1959, Dimond et al 1958) decided to test the rationale by carrying out sham operations to incise the skin and expose the arteries in some patients while proceeding with the full ligation in others. The patients and their physicians did not know who had the true operation and who had the sham. The majority of both groups of patients showed great improvement in the amount of reported pain, in their walking distance, in their consumption of vasodilating drugs and some in the shape of their electrocardiogram. The improvement in both groups was maintained over six months of observation. (No such trial would be permitted today for ethical reasons, although these tests were carried out for the ethical reasons of the day at Harvard and the University of Pennsylvania.) The interest here is not only the evident power of the belief that therapeutic surgery had been completed but that improvement was sustained for at least six months, in spite of the general belief that placebos have a brief and fading action.

The second example is the work of Hashish et al (1988) who examined the effect of ultrasound therapy, which others had found to be the equal of steroids in reducing pain and jaw tightness (trismus) and swelling after extraction of wisdom teeth. To determine the effective level of ultrasound, they set intensity at different levels in a manner which was unknown to the patient and the therapist. When the machine was set to produce no ultrasound, there was a marked beneficial effect, even superior to the results of the normally used intensities. Naturally disturbed by the apparently bizarre finding, the experimenters wondered if the therapeutic effect was produced by the massage of the injured area coincident with the application of the ultrasound. They therefore trained patients to massage themselves with the inactive ultrasound head with the same movements used by the professionals. This was completely ineffective. Evidently, the therapeutic phenomenon required an impressive machine and someone in a white coat to transmit the effect, even though the emission of ultrasound was not required. I introduce this particular example, chosen from many, because the placebo therapy not only reduced the pain report but also improved the ability to open the mouth and reduced the swelling.

The reduction of pain will suprise those people who consider pain as a reliable and inevitable sensation associated with tissue damage. However, there are others who would categorize pain as a mental perception and therefore as subject to error and manipulation. These two attitudes are practical examples of the Cartesian dualistic divide, where sensation is the consequence of the working of a body mechanism while perception is a mental process. There are others who will argue that this division between body and mind is a historical artifact produced by a muddle of academic, religious, introspective argument. Whichever attitude is taken, surprise should remain that the placebo also affected the contraction of jaw muscles normally attributed to a reflex action in the flexion reflex category which loops through the medulla. Furthermore, the placebo affected the swelling, which is a classical component of the local inflammation triggered by local damage.

Four reasons for the discomfort provoked by the topic

Quackery

From the 18th century, the word placebo became attached to quackery. As a rational medicine developed, placebo could be used as a word to hammer Burton's 'empirics and silly chirugeons'. Beyond this, even the rational physicians were not above the use of a placebo as a form of deception, either for diagnostic purposes or to get rid of unwanted or unprofitable patients. This, in turn, provoked the ethical and practical discussion of whether the doctor–patient relationship would survive the discovery by patients that doctors used deception on occasions. This debate on the role of truth-telling and paternalism in the clinic continues (Rawlinson 1985) with discussion of such phrases as 'the benevolent lie'. The ethical problem extends to clinical trials. If it is the doctors' duty to do their therapeutic best, how can they suggest that the patient should submit to a comparison of one therapy which the physician believes to be powerful versus another they believe to be less effective? 'Informed consent' by the patient does not solve this ethical question, it merely recruits the patient to join in the doctor's dilemma. As awe and trust by the patient for the paternal doctor fade, so does the frequency of informed consent and of the placebo response. In 1807 Thomas Jefferson wrote 'One of the most successful physicians I have ever known has assured me that he used more bread pills, drops of coloured water and powders of hickory ashes than of all other medicines put together. . . I consider this a pious fraud'.

A tiresome and expensive artifact

A considerable fraction of the huge cost of clinical trials for a new drug resides in the legal requirement for a placebo trial. When a new idea has been developed

by a clever research team, one has sympathy when their enthusiasm has to be contained while trials are in progress which have an apparently obvious outcome to the enthusiasts. Not only is the expensive delay assigned to the fault of a meddling bureaucracy, but the existence of a fraction of patients who show placebo responses is considered to be of no intellectual interest but simply an intrusion in the search for true mechanisms.

One attractive short cut is to compare the new therapy with an established one without a placebo stage in a cross-over trial. This does not address the possibility that both therapies are placebos. The cross-over option is particularly favoured in those therapies such as surgery or psychotherapy where there is no legal requirement for placebo trials. Often an alternative therapy is not available or is so well known to the patients that it would be impossible to recruit volunteers to a placebo trial. An example is a massive study of long-term consequences of headache and backache after epidural anaesthesia during labour (MacArthur et al 1992) where the authors call for a randomized study to confirm their results. It is obvious that there is no alternative therapy which would be comparable in the mind of a patient with epidural anaesthesia. Furthermore, there is a myriad of cultural, educational, social and medical reasons for a mother accepting or rejecting the offer to be assigned at random to one or another therapy, one of which was epidural anaesthesia. Given the ethical and practical problems in assessing the apparently straightforward question of long-term consequences of an epidural anaesthetic, it is not surprising that the majority of non-pharmaceutical therapies have never been tested or have been tested in very inadequate ways (Koes et al 1991, 1992). For example, in a large-scale survey of thousands of amputees with pain, Sherman et al (1980) identified 40 different forms of therapy but only 15% of the patients were relieved. In a search of the literature, no rigorous trials are reported to justify any of the 40 therapies for this condition. In two surveys of tests for the effectiveness of manipulation, osteopathy and chiropracty for pain, the great majority were shown to be inadequate, while the acceptable trials produced contradictory answers (Koes et al 1991, 1992).

A question of logic

The very mention of a placebo trial is likely to be taken as a hostile questioning of the logic on which a therapy is based. To request an investigation of the placebo component which is an inevitable part of any therapy is to invite anger. Anger confuses the question of whether something should work with the question of whether it does work. Too bad.

The reality of the senses

Everyone assesses their own sanity by cross-checking their sensation with objective reality. On the rare occasions where there is a mismatch, special names

are applied—hallucination, illusion, delusion, madness, drunkeness, etc. For anyone, there is a simple intuitive sense apparent on reading Descartes (1644): 'If for example fire comes near the foot, the minute particles of this fire, which you know move at great velocity have the powers to set in motion the spot of skin of the foot which they touch, and by this means pulling on the delicate thread which is attached to the spot of the skin, they open up at the same instant the pore against which the delicate thread ends just as by pulling on one end of a rope one makes to strike at the same instant a bell which hangs at the other end'. It seems so reasonable that we should possess sensory mechanisms which represent the state of the world as reliably as the tolling of the bell represents action at the end of its rope. It seems equally reasonable that we should possess a separate entity, the mind, which can decide whether to ignore the bell or write a poem about it. Even a philosopher like Bertrand Russell who questioned Cartesian dualism still required a reliable sensory apparatus that generated sensation as the closest representation of events the machinery would permit. Sensation for him was generated by a continuous uncensored flow of information. If this flow was faulty or variable, then even a great cognitive brain would necessarily be faulty. If the sensory apparatus was censored or corruptible, then sense could become nonsense and reality an individual construct of a particular mind. We have many reasons and facts which lead us to reject that conclusion. We trust our senses, the five senses of Aristotle. Pain appears to us as the sensation provoked by injury. A broken leg provokes an appropriate sensation and location of pain. Placebos in no way affect the leg and its fracture but modify the sensation of pain and its perception. No wonder the topic provokes a sense of discomfort.

Diversions generated to avoid a consideration of the nature of placebo responses

When doctors who are not involved in a therapy under trial learn that it turns out to be a placebo, they howl with laughter. When you are the subject in a trial and discover that you have reacted to a placebo, as I have, you feel a fool. When you are the proponent or inventor of a therapy, whether based on contemporary rationale or old-fashioned faith, you are resentful of the need for placebo testing. If the test reveals a substantial placebo component in the response, diversions are created to eliminate consideration of the placebo effect. These add to the four general reasons for discomfort with the effect.

The placebo differentiates between organic and mental disease

This is the most dangerous and cruel attitude which has been used by physicians and surgeons when they detect placebo responses. An example is shown in the reaction of the profession to the true or sham operation on the internal mammary artery described above (Cobb et al 1959, Dimond et al 1958). Amsterdam et al

(1969) describe patients with angina in whom there appears to be an adequate circulation in the coronary arteries. It is then immediately assumed, without evidence, that these are the patients who would respond to a placebo while those with true cardiac ischaemia could not. This idea had already been suggested by psychiatrists using the phrase 'somatic hallucination' (Farrer 1964). Clearly, this approaches the diagnosis of hysteria (Merskey 1989), although in hysteria, the somatization fails to imitate any known organic disease so that the alert diagnostician can differentiate hysteria from the condition it mimics. Here we have the proposal that some patients mimic an organic disease so precisely that a diagnostic test, the placebo, is needed to separate the two classes. The proposal is very attractive to those who seek an absolute separation of organic from functional disease and who believe that every true pain is precisely causally related to an observable organic lesion. The proposal is dangerous nonsense if one considers the hundreds of papers, of which 986 are reviewed in Turner et al (1980), where placebo responses are described in patients suffering pain appropriate to a diagnosed overt organic lesion, such as postoperative pain or cancer.

I will simply relate two illustrative anecdotes. A patient with classical causalgia following a near miss on his sciatic nerve by a bullet had responded to a saline injection interspersed in a regular series of morphine injections. A very senior orthopaedic surgeon concluded that there was therefore nothing wrong with the man, by which he meant there could be no causative lesion in this surgeon's territory of interest, i.e. peripheral nerves and bones, and therefore this was a mental condition as proven by the placebo response. The patient's pain and the vascular signs disappeared with a sympathectomy of the leg, a procedure of which the patient had no knowledge or expectation. This patient's pain was caused by a peripheral nerve lesion and cured by a peripheral lesion. The second anecdote is related by Professor Collins who became head of neurosurgery at Yale. In a forward hospital in Korea, while operating on a series of casualty admissions, he began to suffer severe abdominal pain which was obviously acute appendicitis. Faced with extreme emergency casualties, he ordered the theatre sister to give him an injection of morphine. His pain subsided and he completed the surgery, after which he himself became a patient and his inflamed appendix was removed. Returning to duty after his recovery, he was leafing through the operating room report book when he came across the sister's entry, 'Major Collins ordered a 15 mg morphine injection so that he could continue operating but, since he appeared distressed, I thought it best to give him an intramuscular injection of saline'.

The placebo is the equivalent of no therapy

This is clearly not true. The placebo has a positive effect. If cancer patients receive narcotics at regular intervals, the secret substitution of a single saline

injection in the series of morphine injections results in the relief of pain and other signs and symptoms in the majority of patients. Furthermore, the time course of relief imitates that produced by the administration of the narcotic. The saline injection is not the same as missing an injection, since the placebo produced a decrease of pain while missing an injection would be followed by an increase of pain.

The positive effect of the patients' belief that some therapy is in progress makes it extremely difficult to investigate the natural history of a disease which is not influenced by some form of medical intervention. On rare occasions, it is practically and ethically possible to disguise therapy so that the patient does not know that anything is happening. For example, it may be possible to secrete a drug in orange juice which is routinely provided or a drug may be clandestinely injected into a long intravenous drip line out of sight of the patient. Such elaborate plots have been used, but are obviously limited in most practical trials and raise difficult ethical problems. One scheme to discover the natural history of a disease is simply to leave a group of patients on the waiting list, while treating other groups with true or placebo therapies. There are obvious limits, depending on the society and culture, which determine how long a patient will patiently remain waiting. The richer and/or more aggressive patients or those who are in particular misery remove themselves from the waiting list and go to another doctor, thereby tilting the nature of the remaining list of patients.

A common tactic to obtain the natural history is to study retrospectively the course of the disease in patients before the therapy under study was available. This method is so full of problems that many journals now refuse to publish such studies. We can observe an accumulation of the problems of drug testing if we consider how to test a new therapy for AIDS (acquired immune deficiency syndrome). It is generally believed that the demographic focus of AIDS in the United States has shifted from gay whites to poor blacks. We can see the precise figures for such a move in a very different country in the careful figures from a very wary South African government department (Department of National Health and Population Development 1992). Until 1988, the great majority of cases of AIDS occurred in gay white men. From 1989 to 1992, the number of new cases of AIDS in white men declined. During that period there was a steady large increase in equal numbers of black men and women. Over the entire period from 1982 to the present, only eight cases of AIDS have been diagnosed in white women, four of whom had received infected blood transfusions. Clearly, the distribution is changing so rapidly that a retrospective control would be useless. Therefore let us consider the problem of how to test a new AIDS therapy. We must remember that before a trial started, the media publicity would have informed the public that a remedy had been discovered. Who in these circumstances would volunteer to take part in a placebo-controlled trial? The answer is that a small number of honest and poor people would take the 50 : 50 chance that they would get the new drug at no cost. The rest would buy, beg,

borrow or steal for the drug. This would leave the control group as an odd minority. Even they may not be reliable, because some members of just such a control group in New York have been found, by blood testing, to be buying the drug under trial on the black market. We need new and subtle methods to measure the three quite separate factors—natural history, placebo response and specific response (Finkel 1985).

A fixed fraction of patients respond to placebos

This myth is widely stated in papers and textbooks, with the figure of 33% being commonly quoted. The idea is to label a fraction of the population as mentally peculiar. Where these sources quote the origin of the myth, they refer to Beecher (1955) who gives the figure of 35.2%. However, this figure is an average of Beecher's own eleven studies, each of which varied widely from the average. Double-blind studies show the fraction of placebo responders varying from close to 0% (Tyler 1946) to near 100% (Liberman 1964), depending on the circumstances of the trial. Clinical pains are associated with a larger number of placebo responders than experimental pains (Beecher 1959). The subtlety of the conditions has commercial as well as theoretical interest. Capsules containing coloured beads are more effective than coloured tablets, which are superior to white tablets with corners, which are better than round white tablets (Buchaleq & Coffield 1982). Beyond this, intramuscular saline injections are superior to any tablet but inferior to intravenous injections. Tablets taken from a bottle labelled with a well-known brand name are superior to the same tablets taken from a bottle with a typed label. My favourite is a doctor who always handled placebo tablets with forceps, assuring the patient that they were too powerful to be touched by hand. More seriously, I will discuss the conversion of experimental subjects to placebo responders (Voudouris et al 1989, 1990). There is no fixed fraction of the population that responds to placebos.

Placebo responders have a special mentality

This proposal is an extension of the fixed-fraction myth. It proposes that there are groups in the population with distorted mental processes which lead them to confuse true therapies with placebos. For those who cannot imagine that a normal person would ever make such a mistake, the idea is attractive. It was first proposed by Beecher (1968) and promptly dropped. With the rise of personality psychology, there were any number of pejorative mental tendencies which could be detected in the population by the analysis of the answers to questionnaires. Some of these seemed attractive labels to hang on those who responded to placebos to differentiate them from the normal subject who would never make such a silly mistake. These labels include suggestible, hypnotisable, neurotic, extrovert, introvert, acquiescent, willing to please and unsophisticated.

For anyone who rates high on masochism in a personality questionnaire, I suggest they wade their way through the 36 papers on the topic in Turner et al (1980) and the many more in White et al (1985). Most papers report no correlations with personality type and the rest are contradictory.

Pain is a multidimensional experience and the placebo affects only a part

Beecher (1959) made an intuitive introspective commonsense division of one's personal reaction to pain as having two separable dimensions: one deals with intensity and the other with reaction. This is reminiscent of Cartesian sensation followed by perception. Melzack & Casey (1968) even assigned different parts of the brain to create these two dimensions, which gave a new respectability to this ancient idea. Melzack & Torgerson (1971) then analysed the way in which people used words about pain and derived three dimensions: sensory, affective and evaluative. From this, the widely used McGill Pain Questionnaire evolved. By now, four dimensions have been isolated (Holroyd et al 1992). Gracely et al (1978) and Gracely (1979) examined the placebo response to discover if all dimensions of pain were equally involved. They used volunteer experimental normal subjects who received gradually rising electrical shocks to the teeth. The subjects were asked to rate separately the intensity of the pain and the unpleasantness of the pain, i.e. Cartesian sensation and perception, or Beecher's intensity and reaction, or Melzack's sensation and affect. The subjects were then given a saline injection with the assurance that they were receiving a powerful analgesic. The intensity of the pain was completely unaffected, while at low shock levels the unpleasantness was markedly reduced but at higher intensities was unaffected. This important experiment would seem to bring us back to the most classical position: sensation as a body mechanism is unaffected by a placebo at any stimulus level. Minor unpleasantness as a mental perception is affected by the mental suggestion implicit in the presence of a placebo. When the stimulus intensity rises, the appropriate unpleasantness perception regains its proper place, in spite of implied suggestion from the placebo. These clear experiments would seem to remove the mystery from the placebo and to return the entire subject to classical dualism. Gracely et al (1978) went on to show that diazepam, a tranquillizer, could produce exactly the same effect.

Up to this point one could say that the experiments support a particular version of Cartesian dualism in which there is a reliable sensory apparatus unaffected by these manipulations and that sensation is observed by a mental apparatus which assigns unpleasantness to the pure sensation and which is subject to suggestion and to tranquillizers. However, Gracely et al (1979) went on to investigate the effect of fentanyl, a narcotic, on the same type of pain and the result is summarized in the title 'Fentanyl reduces the intensity but not the unpleasantness of painful tooth sensations'. This abolishes the idea that a reliable sensory apparatus feeds a dependent mental apparatus which assigns

unpleasantness. The three experiments taken together suggest that there are two separate dimensions, intensity and unpleasantness, which can be manipulated independently. We should now ask if the placebo result, i.e. intensity is unaffected but low level unpleasantness is affected, can be taken as a general statement about analgesic placebos. The first prediction would be that placebos would work on minor pains but not on severe pain, but that is precisely the opposite of Beecher's observations (1955) and of those of Lasagna et al (1954). The second prediction is that patients responding to a placebo would report the pain intensity unchanged while the unpleasantness was relieved, but patients with migraine or postoperative pain or cancer report relief of both aspects. Even in experimental situations, both threshold and intensity are affected by placebos (Voudouris et al 1989, 1990). My conclusion is that the identification of distinct categories of pain experience is a valid and useful aspect of pain study but that the placebo effect can change these dimensions separately or together, depending on the circumstances of suggestion, expectation and instruction.

The placebo response is produced by endogenous narcotics

The publication of this statement by Levine et al in 1978 had an enormous and lasting impact. It gave the placebo instant respectability in 20th century terms and partially liberated it from those doubts and denials I have listed above. The logic of this reasoning for the admission of the placebo to polite society is zero. If a newspaper headline read: 'Scientists discover the origin of music and poetry' followed by an article showing that music could not be performed when curare prevented the effect of acetyl choline released from motor axons, one would not be overwhelmed by the insight into the nature of music and poetry. Similarly, it is not clear what insight into the overall placebo phenomenon is provided by showing that some link in the machinery involves endorphins.

In addition, there are several problems with the original experiment which reported that high doses of naloxone, an opiate antagonist, abolished the placebo reduction of pain following wisdom tooth extraction. There are three reasons the experiment is complex and difficult. First, the pain did not have a steady baseline but was naturally rising and falling during the period of observation. Second, while naloxone by itself has no effect when there is no pain (El Sobky et al 1979), in the presence of pain, naloxone by itself exaggerates the pain, depending on the dose (Levine et al 1979). Third, some subjects were excluded from the analysis for reasons which are questionable. This difficult experiment has not been repeated, but Mikic & Binkert reported at the 2nd World Congress on Pain in Montreal in 1978 that they were unable to show an influence of naloxone on the placebo effect on pain caused by cold. Gracely et al (1982) also examined the effects of naloxone and placebos on the pain of tooth extraction and concluded that the naloxone effect was independent of the placebo effect. The careful studies of Grevert et al (1983) have been quoted as supporting

Levine et al (1978), but that is not justified. They studied the effect of naloxone on a placebo reduction of experimental ischaemic pain. Each subject was tested on three occasions at one-week intervals. On the first two tests, naloxone had no effect on the placebo response, but by the third week the high dose of naloxone produced a partial decrease of the placebo response. I believe the most generous reading of these four experiments is that the question remains open.

The placebo effect may be dissected away to reveal the pure therapeutic action

For this to be true, the therapeutic effect of an active compound would have to be free of its own additional placebo component. Strong evidence shows that the two responses are not separable in practical tests. In an extensive series of tests on postoperative pain, Lasagna et al (1954) identified placebo reactors and non-reactors. They then gave a fixed dose of morphine to the two groups and found an adequate analgesic response in 95% of the placebo reactors and only 55% of the non-reactors. A much more subtle problem was revealed by Beecher (1968) on examination of the matrix of results from double-blind cross-over studies of morphine versus saline. If the first administration contained morphine, the patient learned that this trial involved powerful medicine and tended to give a strong response to the second administration which was saline. If the first test dose was saline, the response to the second which contained morphine was weak. It is obvious that this problem will also affect the results of trials where the relative effects of two active compounds are being compared. There will be a carry-over effect of the first trial on the results of the second.

It is apparent that the patient or subject is searching for subtle hints of what to expect and that these expectations affect responses. This raises the question of the comparable nature of the active test and the placebo test. It does not take a connoisseur to distinguish intravenous morphine from saline, because the morphine produces such obvious immediate side effects. This problem has led to the use of placebos that produce some obvious effect, such as vasodilatation, which are assumed to have no direct therapeutic effect but give the subject an impression of receiving powerful medicine. The introduction of active placebos produces a series of problems: the placebo and active compound rarely precisely mimic each other; the specific inactivity of the placebo is questionable; the patient may find the placebo's effects distasteful. These problems apply even more to other forms of therapy. What is a comparable manoeuvre against which to test acupuncture? The nature of acupuncture is well known to 90% of the world's population.

Because, as we shall see, it is the expectation of the subject which is crucial, the obverse is the question of secrecy. It is assumed in therapeutic trials that the subject is not aware of the expectation of the proponent. Can that be achieved in practice? Sometimes the secrecy is shattered in obtaining consent: 'We would like you to help us in a trial of a new, safer form of aspirin'. Almost always,

the person who administers the therapy, who may not know which pill is blank and which is 'true', will be aware of the general nature of what is being tested. This person's expectations can be covertly infectious. Patients talk to each other and reach a consensus; the strong effects of this covert expectation are shown by Evans (1974). He examined the relation between the relative effect of a range of analgesics versus placebos in 22 published double-blind trials. If the placebo effect was independent of the therapeutic effect, the placebo fraction of responders would have been the same in all trials while the drugs ranged in a series of therapeutic potency. The results all show that the stronger the drug, the stronger the placebo response. Evans divided the pain reduction produced by the placebo by the reduction produced by the drug. The answer is a fixed 55–60% over the entire range from weak to strong analgesics. So much for the blindness of these double-blind trials. So much for the clear separation of placebo and therapeutic effects.

I have described seven reasons why we need to avoid diversions, which are seven reasons why we need to consider the placebo effect with respect as a powerful phenomenon.

Classes of explanation

Affective

Gracely et al (1978) propose that the placebo effect works on the unpleasantness of pain while leaving the intensity dimension unaffected. I gave reasons above to believe that their experiments represent a special case which does not apply universally, especially in clinical cases. Evans (1977) proposes that the placebo operates by decreasing anxiety. However, the results show that there is a weak and variable interaction with various types of anxiety and it is not clear that anxiety reduction is not a component of the placebo effect rather than the cause of it.

Cognitive

By far the commonest proposal is that the placebo effect depends on the expectation of the subject. There is nothing subtle about this. Placebo reactors can be identified before the trial by simply asking the subject what they expect to be the outcome of the therapy. Those who doubt do not respond to the placebo, while those with high expectations do (reviewed by Bootzin 1985). Lasagna et al (1954) investigated many aspects of postoperative patients who responded to placebos and to analgesic drugs and conclude: 'a positive placebo response indicated a psychological set predisposing to anticipation of pain relief'. They add: 'It is important to appreciate that this same anticipation of pain relief also predisposes to morphine and other pharmacologically active drugs'. In a

trial of two drugs versus placebos on one hundred patients, Nash & Zimring (1969) tested specifically for the role of expectation. The two drugs had no effect which would differentiate them from the placebo, but there was a strong correlation between the measured expectation and the placebo effect. Expectation is given a number of related names, such as belief, faith, confidence, enthusiasm, response bias, meaning, credibility, transference, anticipation, in 30 of the papers in the bibliography of Turner et al (1980).

Expectation is a learned state and therefore young children do not respond to placebos as adults do, because they have had neither the time nor the experience to learn. Similarly, in adults, the learning of expected effects will depend on culture, background, experience and personality. A desire to believe, please and obey the doctor will increase the effect while hostility decreases it. Obviously, part of the expectation of the patient will depend on the expectation, enthusiasm and charisma of the therapist and there are many reports on this doctor–patient interaction. Expectation in a laboratory experiment may be more limited than in a clinical setting, which may explain why rates and intensities of placebo effects tend to be less in the laboratory than in the clinic (Beecher 1959).

Conditioning

There are many reports of drug anticipatory responses in animals (Herrnstein 1965, Siegel 1985). These come in two forms. In the first, the animal has been given one or more trials on an active drug and is then given a saline injection; it proceeds to mimic the behavioural or physiological response which was observed after the active drug. In the second type, the animal mimics the actions which it mobilizes to neutralize the effect of the active compound. For example, if animals have experienced a series of injections of insulin which lower the blood sugar, a saline injection in the same setting as the insulin injection results in a rise of blood sugar which would be one of the animal's reactions to counteract the insulin-induced decrease (Siegel 1975). In cultures not raised on *Winnie the Pooh*, *The Wind in the Willows* and *Watership Down*, it is customary to deny animals the luxury of cognitive processing and to ascribe such phenomena to classical Pavlovian conditioning.

This led to the proposal that the human placebo response had the characteristics of a conditioned response (Wickramasekera 1980, Reiss 1980). The idea is that active powerful drugs produce a powerful objective physiological response in the same manner that food produces salivation, the unconditioned stimuli and responses. However, giving the drug is inevitably associated with a pattern of other stimuli, such as a hypodermic injection. It is proposed that these are the equivalent of unconditioned stimuli coupled with the conditioned stimulus. It is then proposed that if these incidentally coupled stimuli are given alone, they will provoke the same response as the original drug, just as in the dog, coupling a bell with food eventually leads to the ability of the bell by itself

to provoke salivation. The similarity goes beyond the proposed production of a conditioned response. If a placebo is given repeatedly in some, but not all, trials, the effect declines. This is a characteristic of Pavlovian responses, where simple repeated ringing of the bells leads to a steady decline of the salivation unless the conditioning is reinforced by occasional coupling of the bell with food.

All such comparisons between widely differing processes lead to argument about similarities and differences, identities and analogies (Wall & Safran 1986). However, the idea led to a series of clever experiments by Voudouris et al (1989, 1990). The first stage was a repeat of a type of trial which had been reported many times before. Volunteer subjects were given rising electric shocks and the current was established, in full view of the subject, at which the shock became painful and the level at which it become intolerable. Then a bland cream was rubbed on the area, the subjects were assured that it was a powerful anaesthetic, and the shock trial was run a second time. A small fraction of the subjects demonstrated a placebo response by reporting pain and intolerable pain at a higher shock level than they had on the first trial. This established the placebo response rate in these circumstances. They then started again with a new group of subjects and determined their threshold and tolerance shock levels. The cream was applied and, now came the clever and novel part of the experiment, the strength of the electric shocks was secretly reduced, unknown to the subject and observer. When the trial was now run, the subject observed that much higher numbers on the shock machine were achieved before pain was felt and before the pain reached the tolerance limit. These subjects believed that they had tested on themselves the truth of the remarkable anaesthetic properties of the cream. Next, after one such apparent demonstration of the efficacy of the cream, a trial was run in the original conditions, i.e. the strength of current was returned to its original level. The cream was put on and the shock level raised. On this trial, large numbers of the subjects became placebo reactors. The only difference in these newly produced placebo responders was that they had 'experienced' in some fashion the apparent anaesthetic properties of the cream. Clearly, this result can have important practical implications. Whether the change in the subjects was cognitive or conditioned must remain an issue for debate and further experiment. Brewer (1974) concludes that 'there is no convincing evidence for operant or classical conditioning in adult humans' which is free of cognitive awareness of the situation. It may be that the passionately maintained differences between cognitive and conditioned responses will collapse.

Response-appropriate sensation

I wish to introduce a novel proposal, which is that certain classes of sensation are locked to the response that is appropriate to the situation, in contrast to the classical view that sensation is always locked to a stimulus which provokes it. I refer *only* to certain types of body sensation and not to those sensations

related to the outer world, such as sight and sound, where psychophysics shows a precise lawful relation between stimulus and sensation. However, the psychophysics of pain differs wildly from that of other senses (Sternbach & Tursky 1964). This special class includes pain, hunger, thirst, vertigo, fatigue, sleepiness, feeling too hot and too cold. In this class of sensations, each member is associated with disease where the sensation is not coupled with the appropriate stimulus. For pain, this is a major clinical problem to be discussed below. This proposal for a separate class of sensations has been approached in a series of steps (Wall 1974, 1979).

In diseases where overt pathology is an integral part of the diagnosis, such as osteoarthritis, the amount of pain is poorly related to the amount of pathology. In other diseases, such as angina pectoris, an appropriate evocative pathology, such as occluded coronary arteries, is obvious in some cases but not all. In other painful conditions, no appropriate peripheral pathology has been identified. These include trigeminal neuralgia, migraine, atypical facial neuralgia, temporo-mandibular joint syndrome, post-encephalitic myalgia syndrome and fibromyalgia. The most extreme example of an uncoupling of pain from injury occurs in emergency analgesia following abrupt injury. Beecher (1959) reported that 70% of soldiers admitted to a forward hospital with severe battle injuries did not complain of pain. In the less dramatic setting of a city hospital, 40% of patients admitted after the common accidents of civilian life reported no pain at the time of the accident (Melzack et al 1982); another 40% reported high levels of pain. There was no obvious relation between the location or severity or nature of the injury and the amount of pain reported at the time of the injury. Three characteristics of this analgesia are crucial to its understanding. (1) The patient is usually fully aware of the injury and its consequences but describes the initial sensation in neutral words, such as 'blows' or 'thumps'. (2) In hospital, the analgesia is precisely located only to the original injury and does not apply to subsequent stimuli such as the introduction of an intravenous line. (3) By next day all are in the expected pain. Similar behaviour is observed in animals after injury (Wall 1979).

While the body sensations under discussion appear poorly related to a provocative stimulus, each is inevitably linked with attention and with a predictable response. For hunger, eating; for thirst, drinking, etc. For pain, three phases of response are observed: to attempt to avoid further injury, to seek aid and safety, and recovery from injury (Wall 1979). The third phase includes immobilization of the painful part, avoidance of contact on the painful area, withdrawal and sleep. All three response patterns are observed in animals as well as in humans.

If, then, pain and the other sensations discussed are variably linked to the provocative stimulus but reliably locked to the response, would it not be reasonable to propose a brain mechanism by which the brain analyses some internal body states in terms of the biologically relevant behaviour and that

certain sensations signal the outcome of that analysis rather than the input on which the analysis was based? Just such a brain mechanism has been explored by the ethologists who followed Hess, Tinbergen and Lorenz. In these animal schemata, the brain continuously monitors the flow of information from the internal and external sensory apparatus. Next, a biological priority is assigned to a fraction of the input and the appropriate motor pattern is released. Let us propose that humans, too, incorporate such an apparatus in their brains and that the initial stages do not necessarily intrude on consciousness. Let us propose further that conscious pain appears only after the priority assignment stage and that pain is sensed consciously at the same time as the release of the motor pattern. The ethological motor patterns of vertebrates are *not* fixed action patterns or reflex discharges; they require reference to the sensory system in order to shape the correct response. The combination of an empty stomach and the sight of a nearby bill release the herring gull pecking motor pattern. However, the herring gull chick still needs to use its sensory apparatus to locate the red spot on the mother's bill in order to peck at it. In other words, there are two sequential uses of the sensory input. The first is to assign priority and the second to guide the motor behaviour. It is proposed here that pain appears as a conscious phenomenon only in the second epoch of sensory analysis after the period during which priority was established but consciousness is not alerted.

For pain and the placebo response, I propose that before the placebo, the unconscious priority decision mechanism had assigned priority to the motor pattern and sensation of pain: after the placebo, which is a stimulus with its learned powerful association with pain relief, the unconscious priority decision mechanism reverts to selecting a non-pain state. This new situation assigns a lower priority to pain and allows the release of the next most biologically appropriate pattern. This two-stage analysis process could also provide a rational basis for the other apparently paradoxical absence of pain, emergency analgesia. Pain is the obvious reaction to overt injury but other actions and sensations may take precedence. For the soldier in action, impending death has the well known property of 'concentrating the mind' and much more elaborate life-preserving actions and reactions take precedence over the reaction to localized injury. This begs the obvious question of why one sensation should take precedence over another. Why could they not both be felt simultaneously or at least rapidly alternating? The probable answer reinforces the linking of this type of sensation to motor pattern. It is not biologically permissable to release two motor patterns simultaneously. It would be disastrous to attempt to advance and retreat at the same time. Animals in ambiguous situations exhibit what Tinbergen called displacement activity. A herring gull in a threat posture suddenly switches on a nest building motor pattern and rips up tufts of grass. Obviously, sensation should not be considered to result from an all-or-none switch. Priorities would have a strength and a duration which would be mirrored in the strength and persistence of attention and of sensation.

For an hypothesis to be useful it has to be more than an analogy (Wall & Safran 1986), it has to be both testable and deniable. For the placebo response, this requires probing inside the brain, but that itself requires a definition of what would be the object of the search, which leads me to the final section.

The philosopher's brains

Anyone thinking about thinking inevitably produces a scheme that incorporates cause and effect. Experimentalists also require a plan on which to organize their questions and, usually implicitly without statement, adopt one of the philosophical schemata. With almost vanishing rarity, the experimental findings have affected philosophical thought. There are four classical plans upon which experiments to discover the nature of sensory processing have been based and I wish to propose a fifth for the future. The four plans are complementary and each has generated undoubted facts that have to be incorporated in any plan.

Dualism

This scheme remains the main basis on which most neurophysiology is based. It predicts that identifiable components of the brain will reliably detect, transmit and deliver specific fractions of sensation. My own and many others' inability to detect any such system which could be reasonably labelled a pain system led me to reject the plans as a plausible generator of the sensation of pain (Wall & Jones 1992). Light pressure on the skin usually provokes a sensation of touch but in other circumstances, i.e. tenderness, the same stimulus to the same skin is very painful. The plasticity of the relation of the stimulus to response and the changeable properties of the neurons made it impossible to view this sensory system as line-labelled, modality-dedicated and hard-wired as required by the Cartesian system. From Descartes on to Eccles and Popper, an absolute separation is made between the reliable body machinery which produces sensation and the subsequent mental process of perception (Fig. 1).

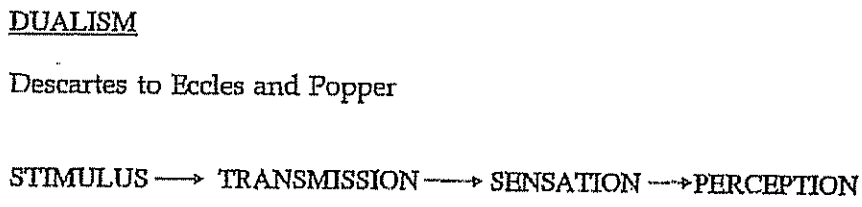

FIG. 1. Dualism.

Hierarchies

Two hundred and fifty years after Descartes and contemporary with Darwin, a scheme for subdivision of the nervous system into higher and lower levels was introduced (Fig. 2) but it has been interpreted incorrectly in three ways. First, it has been taken to mean that 'higher' is the same as 'more recently evolved'. This, in turn, is taken to justify the dogma that the mind is in the cerebral cortex. What a leap (in the dark)! Second, while evolution is much discussed in Hughlings Jackson's writing and while his guru Spencer originated the phrase 'survival of the fittest', they used evolution to mean something quite different from Darwin. Spencerian evolution relates to thermodynamics and to entropy and is therefore reversible, while Darwinian evolution is not reversible. The third incorrect interpretation was a trivialization that has dominated the use of the scheme in the 20th century. Three crucial discoveries had been made by Jackson's time. There are anatomically separate inputs and outputs to the central nervous system (Bell and Magendie). There are anatomically separate input and output pathways within the central nervous system (Brown–Sequard). There are reflex pathways within the spinal cord which link inputs and outputs (Sechenow). Even the simplest neurologist and the most sophisticated text book writer could cope with these three ideas. Therefore they took Jackson and his subtle followers to mean that there was a short reflex pathway which runs through the spinal cord, a longer one through the brain stem and the longest one which looped through the cortex. In fact, Jackson and Sherrington were very specific that there were internal loops connecting the various levels, which makes a considerable difference from a simple set of reflex loops. Jackson's greatest neurological discoveries came from epileptics. In the commonest form of grand mal epilepsy, the convulsive phase of the attack is preceded by a sensory aura in which the patient has a sensory experience. This can vary among patients from a simple tingling on one finger to an elaborate scene with people, music and a landscape. These are not hallucinations in the sense that the patient believes they are actually happening. On the contrary, the patient is angry and terrified because they know they are about to have a fit. Auras are brilliantly described by Dostoevsky, himself an epileptic, in *The Idiot*. The importance for our present discussion is that the brain is capable of creating virtual reality without reference to or stimulation from the sensory nervous system. This depends on

HIERARCHIES

Hughlings-Jackson and Herbert Spencer to Sherrington

STIMULUS ⇆ SPECIFICS ⇆ INTEGRATION ⇆ HIGHER CENTRES

FIG. 2. Hierarchies.

long-range feedback mechanisms within the central nervous system, which do not reach out into the periphery.

Cybernetics

Claude Bernard was concerned with the maintenance of a stable internal environment. As he and those who followed studied how stability was achieved, they began to realize that a series of components must exist. This was formalized by Norbert Wiener as cybernetics (Fig. 3). First, there had to be an internal standard which was compared with the actual situation. A comparator measured the mismatch between a sensory input which signalled the actual situation and an internal standard which signalled the ideal situation. This mismatch signal was amplified and triggered a series of graded output patterns which, in turn, fed back onto the actual input to reverse its trend and thereby to reduce the mismatch signal. Physiologists have identified many of the components. In cooling, for example, the dropping temperature is the stimulus which deviates from the standard. The mismatch difference signal triggers an orchestrated series of output patterns as the difference grows—vasoconstriction, piloerection, release of thyroid hormone, insulin and adrenaline to increase metabolism, shivering, rigors.

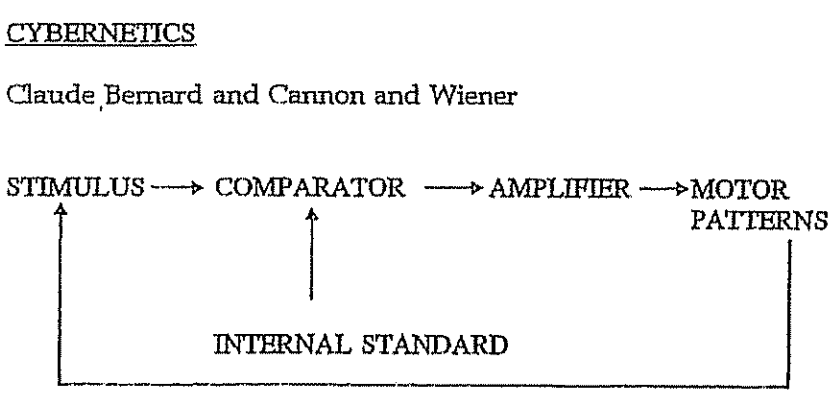

FIG. 3. Cybernetics.

Ethology

This spectacular development of old-fashioned nature study which I have discussed above defined a series of stages between stimulus and response (Fig. 4). The sensory input is used twice, to decide first what to do and then how to do it. In the initial stage, a combination of sensory signals from outside and from inside assigns a priority to one feature in the behavioural repertoire. This

ETHOLOGY

Hess, Tinbergen and Lorenz

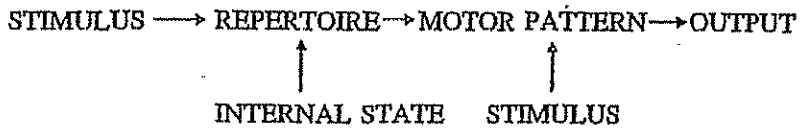

FIG. 4. Ethology.

releases the motor pattern which is most relevant to the biological situation. The successful achievement of this motor pattern requires a second consultation with the sensory system. Where is the enemy, mate, nest or chick and is it being approached on the optimal course? Experimental studies have been very successful in identifying the sensory patterns and the motor pattern generators but less so the priority-assignment mechanism.

Reality–virtual reality

I wish to propose here that advanced brains contain both the Jackson version of a hierarchical system and the Tinbergen–Lorenz version of an ethological system. The ethological component sequence of repertoire–priority–motor pattern contains an inherent fraction of species-specific components heavily modified by experience and learning. This machinery is entirely responsible for the domestic and skilled actions of everyday life and does not involve consciousness. However, on occasions, a combination of internal and external stimuli occur for which there is no biologically appropriate response available in the repertoire–priority–motor pattern system. When this mismatch occurs, an attentional switch diverts the input into a quite different system. Before going further I wish to give two illustrative examples.

The phantom limb has been a challenging paradox for philosophers and neurologists. Descartes was aware that he had set a trap for himself in the very rigidity of his proposed sensory mechanism. He writes (1641) in *Meditations on First Philosophy*: 'It is manifest that notwithstanding the sovereign goodness of God, the nature of man, in so far as it is a composite of mind and body, must sometimes be at fault and deceptive. For should some cause, not in the foot but in another part of the nerves that extend from the foot to the brain, or even in the brain itself, give rise to the motion ordinarily excited when the foot is injuriously affected, pain will be felt just as though it were in the foot and thus naturally the sense will be deceived: for since the same motion in the brain cannot but give rise in the mind always to the same sensation and since this

sensation is much more frequently due to a cause that is injurious to the foot than by one acting in another quarter, it is reasonable that it should convey to the mind pain as in the foot'. The brilliance of Descartes here introduces the idea of the false signal but at the same time has to define the mind as a passive slave of the sensory apparatus. Three centuries later, Bromage & Melzack (1974) considered the results of adding local anaesthetic to nerves supplying a body part. Far from producing signals, these agents block the normal trickle of signals which reaches the brain. A startling phantom phenomenon appears in the area of anaesthesia. This phantom is not an imitation of the real limb, it is more real, swollen and attention grabbing. On the scheme under discussion, the repertoire–priority component of the brain is presented with a sensory input which is simply not in the repertoire. In that situation, the attention switch operates to bring into action the sensation perception mechanism, which, in the absence of a sensory input, creates a virtual limb. Seeking a confirmatory sensory input, the patient visually explores the limb and palpates it and the phantom disappears.

The second example comes from the work of Dubner et al (1981), Bushnell et al (1984) and Duncan et al (1987), which is so startling and novel that it has yet to intrude on theory. They recorded in monkeys from first-order central cells which receive information from nerve fibres from the skin. By all classical criteria, these cells fulfil perfectly the requirements of Cartesian sensory transmission cells—their discharge rigidly and reliably reflects a particular stimulus applied to a unique area of skin. The cells signal in a lawful fashion the location, intensity and nature of the stimulus with such reliability that the signal was the same in awake or anaesthetized monkeys. These workers then trained the animals to use a stimulus in a discrimination task in which the correct response was rewarded. The form of the trial was that the animal was first given a warning signal that the trial was about to begin, then the stimulus was applied and then the animal was rewarded with a drink of orange juice if it reached out and pushed a button if, and only if, the stimulus was of a particular intensity. When the training began, of course, the cell responded only to the skin stimulus and not to the warning signal or any of the other events. However, when the animal had successfully solved the problem and was fully trained, most of the cells produced a brief burst of activity after the warning signal. This novel period of cell discharge mimicked the discharge of the cell which always occurred after the stimulus to be discriminated was presented. This means that the trained brain had created a virtual input which ran over the same pathway as the input provoked by the real stimulus. A precise model of the expected input precedes the input actually provoked by the expected stimulus. The literature contains several examples of this creation of inputs without stimuli in classical and operant conditioning.

Returning to the scheme, it proposes that the brain is capable of generating a virtual reality (Fig. 5). It is further proposed that this experimental theatre is

REALITY - VIRTUAL REALITY

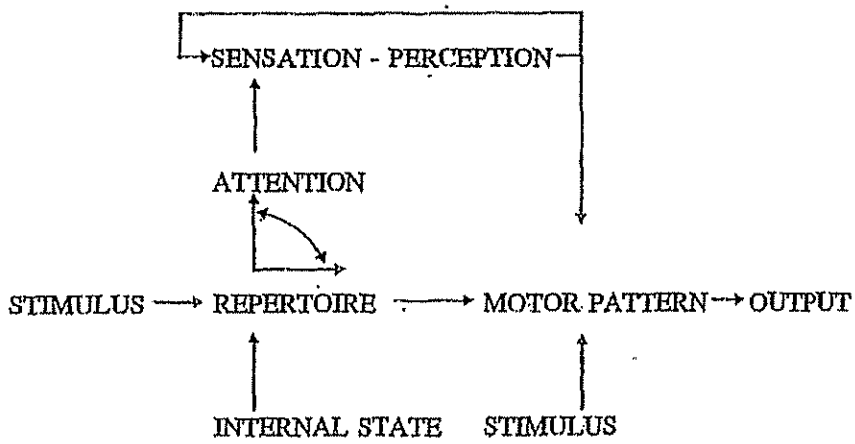

FIG. 5. Reality–virtual reality.

brought into action only when the repertoire–priority system fails to provide a biologically appropriate motor pattern. The Jacksonian reality–virtual reality experimental theatre is simultaneously author, director, stage, actors and audience. In the situation of a fully mastered discriminant task, the expectations of the stage play precisely mimic reality. That is pantomime. In chronic pain, no amount of rewriting or changing of cast and scenery provides a resolution to match and cancel reality. That is tragedy.

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DISCUSSION

Harnad: I would like to generalize what you have described. It is not just placebo that behaves this way. Diabetics will sometimes get into acute hypoglycaemic states: they keep sugar in their pockets, and as soon as they pull the sugar out and lick it, their hypoglycaemia vanishes. This, of course, can't be because of a direct contribution to their systemic glucose levels. In fact, one can achieve the same effects with saccharin. This is also true in ordinary metabolism. The glucostat turns off your hunger well before the requisite homeostasis has been re-established. So it seems that the whole nervous system is geared towards huge anticipatory physiological responses, all based on experience and habit. However, you can very quickly extinguish the remedial effect of licking saccharin by doing it repeatedly without following it with a real increase in blood sugar.

I have two questions. Is there any evidence for chronic placebo effects? Second, is there a possibility that the 33% predictability (if there is some reality to this figure) is anomalous only in the sense that perhaps if a subpopulation is hypnotically susceptible, they don't extinguish placebo effects the way everybody else does?

Kihlstrom: There is no relationship between the placebo response and hypnotic susceptibility.

Harnad: Not the placebo response in general; I am asking about chronic placebo or non-extinction of placebo.

Wall: That was why I gave the example of surgery for angina. The effect of the sham operation remained throughout the six month period of observation. There are many other examples. When an ineffective drug is withdrawn, there is always a large number of patients addicted to the placebo. So there is a chronic placebo effect.

Fenwick: Much depends on our models of explanation. We often have quite the wrong idea of how the system works. The conventional idea of epilepsy is that cell discharges cause seizures, are seizures. What is not asked is: how do these seizures arise? In focal epilepsy, the seizure pacemaker cells are firing all the time, but patients don't have seizures all the time. So what causes the activity of the pacemaker cells to spread into groups of surrounding cells? One important factor is learning—learning to have seizures. There are fascinating accounts in the literature of seizures in cats being conditioned to a flashing light. This is an amazing process: a flash on the retina can apparently produce synchronization of cells around a focus which is not in any way connected to the visual system. Thus, in epilepsy, by a similar mechanism, it is possible to learn both to have, and not to have, seizures. The placebo responses in epilepsy can be explained this way, as alteration of a mental construct. This directly alters the excitability in populations of cells surrounding the epileptic focus, and thus alters the probability of a seizure occurring.

I chose epilepsy on purpose because you frequently get dramatic placebo responses. Some time ago a series of patients at the Maudsley hospital were implanted with cerebellar electrodes. It was hoped that stimulation of these electrodes would stop their seizures. The response from the first patient was excellent, as the stimulation appeared to stop seizure activity. The second patient was equally successful but in a rather different way, and here the placebo response was most important. The electrode array was implanted in the patient's cerebellum and the leads taken down to the chest, but no stimulator was implanted. The patient, without any stimulation, did not have another seizure. This is a maximal placebo response. I think there are very precise mechanisms which underlie this placebo response. Many patients have mechanisms whereby they can stop seizure activity by changing the levels of excitation and inhibition surrounding a focus. In most patients this occurs unconsciously. I suspect it was a similar mechanism that stopped our patient from having fits. There seems to be a close relationship between mind and brain.

Searle: The analogy that you gave with the warning does rather fit the text book story. The suggestion is, habituation affects the physiology in such a way as to create a new circuit. In the case of the warning signal, the warning has the same consequences in the circuitry as the real thing. That would seem to fit the morphine case, where there is a whole set of surrounding stimuli that go with the pharmacology of the morphine. The guy regularly sticks a needle in your arm, and he squirts some stuff in you. According to text book physiology, that's going to create new circuitry. You can activate that circuitry simply by injecting a saline solution. You don't need the pharmacology because the circuit is already there. But, I think you want to say something much more exciting than that. You want to say that the story about the circuitry won't work in any simple way for a first time placebo. Your model of the warning signal won't work for the people who have the placebo operation.

Wall: The placebo stimulus occurs on the background of a long history of the individual's experience of medical treatment. Placebos that work on adults don't work on five year olds. 'Mummy will kiss it better' works on a five year old. That placebo habituates for various reasons (what you think about your mother) and you substitute another set of stimuli as being associated with effective therapy.

In the animal experiment, the animal slowly learned to associate three events: the warning stimulus, the stimulus to be discriminated and the stimulus provided by the reward. After the association is established, the warning signal is followed by nerve impulses in the same cells that respond to the stimulus to be discriminated. The first volley of impulses represent virtual reality created by brain mechanisms followed by a volley representing the reality of an external stimulus.

Gray: But what John Searle has just said remains correct. The animal cases, the morphine injection and the button press can all be understood as classical

conditioning. The only difference depends upon whether the conditioned response is in the same direction as the drug effect—as in the morphine case you described—or whether it is an opponent process counteracting the direct drug effect (Siegel 1983). It is actually very difficult to figure out the conditions which give rise to one or the other, but they are both familiar processes.

I think the issue is whether, when you are dealing with the prestige of a doctor with a white coat who is giving an intravenous injection, that fits the model. It is not a first time placebo, it clearly depends on a great deal of knowledge about doctors and intravenous injections and so on. But it might not be classical conditioning, because those precise circumstances need not necessarily have occurred before in just the way they are occurring now.

Dennett: You can test the classical conditioning hypothesis directly, and rule it out, by administering the placebo or the drug under rigidly controlled, nearly identical stimulus circumstances in which you vary just one parameter. Suppose each time you do it, there is somebody in the room who says something. Sometimes he says, 'The Red Sox lost the ball game last night'. Another time he says, 'I think it's going to rain tomorrow'. The third time he says, 'We have run out of morphine, give him the saline'. Then you see a marked reduction of the placebo effect. It clearly depends on the subject recognizing the meaning of the words.

Gray: That will not work. There were experiments in the 1940s and 1950s which showed semantic conditioning, that is, generalization of Pavlovian conditioned reflexes along dimensions of meaning (Razran 1971). This phenomenon allows one to analyse the effects of a statement such as, 'We have run out of morphine', while remaining within the framework of classical conditioning. I'm not saying that is the way such effects are produced, only that your thought experiment does not rule conditioning out.

Wall: When the placebo effect first became apparent, people said, 'This is clearly a mental process, it's something to do with the perceptive failures of the subjects'. Now you say it's conditioning. I don't think either of those statements is more than labelling an unknown process.

Gray: I'm not saying that. There are some analysed cases that are conditioning.

Searle: The question then is, how do you think it works?

Wall: In the first place, I would like to admit the possibility of generating an effective reality.

Nagel: Is part of your message that ordinary cases of feeling or no longer feeling pain have a much more global explanation than might originally have been thought? Even in the case in which you stub your toe, the picture of the impulse creating a sufficient condition for pain in a localized place is inaccurate, because there too, you are creating a virtual reality.

Wall: I agree.

Humphrey: Why do you think that these phenomena occur more dramatically in the realm of touch than they do in vision? If you sound a warning bell and flash a spot of red repeatedly on the retina, it will never happen that when the bell sounds there is a sensation of red. I like your model of virtual reality, and I would like to be able to generalize it much further than just the pain situation, but it doesn't seem to generalize. What do you think is so special about touch and pain?

Wall: I think you have two types of sensory experiences, one of which implies that you are going to do something, and a second which may be completely neutral. To feel hunger or thirst or pain implies that you are going to try to abolish those sensations. Whereas 'I see a light, I feel touch' can be utterly neutral with no predictive qualities. I propose that the first type is open to manipulation when some other predicted behaviour is more biologically appropriate for the individual.

Kihlstrom: I have always thought the placebo response was especially interesting for the reverse of the conventional way of thinking about the mind–body problem. We usually think about mental states as emerging from physiological processes. In placebo, there is a mental state that seems to alter physiological processes. I don't want to push that too far, but psychosomatic effects of all sorts have that quality.

There is another category of effects that are expectation driven and that are also perceptual in the way that pain is perceptual. We know that expectations have profound effects on things like visual perception. In what sense are these kinds of things different from those sorts of expectation-driven percepts?

Wall: Don't forget, the placebo effect is initiated by an action from the outside. The interesting question is: could one generate a therapy in which the equivalent of a placebo could be generated internally?

Kihlstrom: One most likely could. I was a student of Fred Evans, who showed that the effect of the placebo compared to the active agent was a constant, regardless of the agent to which it was being compared (Evans 1974). Placebo compared to aspirin is 0.54 as effective as aspirin. Placebo compared to morphine is 0.56 as effective as morphine. So if you had a pain that could be effectively treated with aspirin, you could think you were giving morphine and get complete pain relief! Evans suggested a remarkable way of titrating placebo effects to good effect.

Wall: The implications of those results are not precisely what you have suggested. The implications are that it is exceedingly difficult to do a blind experiment in which all clues of expectation are hidden from the patient.

Kihlstrom: I am sure it also disrupts the placebo effect. Because the physician has to believe in what's being given as well as the patient or the treatment will not work.

Marcel: In 1838, Johannes Müller proposed the doctrine of specific nerve energies. That is, the type or modality of your experience would be a function

of the nature of nerve involved, which is sensitive only to a particular type of input. Clearly, this is wrong. The consciously felt modality and type of sensation are at least partly the result of attribution. How far are we willing to push the role of tacit beliefs? This is related to the concept of somatization. How many types of somatization are there? There is most trivially the metaphoric type, where 'pain' is just a metaphoric term. There are also two other senses. First, all sensations felt in the body are mental, in so far as they are felt. The second is due to how a culture contructs selfhood. One culture constructs certain types of mental events as bodily, another constructs them as existential. In the former, you will experience a situation as pain, in the latter as mental suffering (Kleinman 1986).

To what extent are qualitative properties (qualia, sensations) actually a function of certain types of beliefs?

Wall: Hysterics create a sensory state within themselves that they cannot distinguish from reality, unlike the epileptic's aura, which the patient rapidly learns does not reflect reality.

Marcel: It really is felt, it really is a pain. What's to distinguish it?

Wall: I agree it's creating a state which is indistinguishable from what would happen had there been an input. I agree with Libet that the hysteric appears to produce false signals half way down the line. It would be useful therapeutically if we could learn how to produce apparently true signals without there being an input to produce them.

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EXHIBIT D

REVIEW ARTICLE

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Clinical Pharmacology of Tramadol

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Contents

Abstract

Tramadol, a centrally acting analgesic structurally related to codeine and morphine, consists of two enantiomers, both of which contribute to analgesic activity via different mechanisms. (+)-Tramadol and the metabolite (+)-*O*-desmethyl-tramadol (M1) are agonists of the μ opioid receptor. (+)-Tramadol inhibits serotonin reuptake and (−)-tramadol inhibits norepinephrine reuptake, enhancing inhibitory effects on pain transmission in the spinal cord. The complementary and synergistic actions of the two enantiomers improve the analgesic efficacy and tolerability profile of the racemate.

Tramadol is available as drops, capsules and sustained-release formulations for oral use, suppositories for rectal use and solution for intramuscular, intravenous and subcutaneous injection. After oral administration, tramadol is rapidly and almost completely absorbed. Sustained-release tablets release the active ingredient over a period of 12 hours, reach peak concentrations after 4.9 hours and have a bioavailability of 87–95% compared with capsules. Tramadol is rapidly distributed in the body; plasma protein binding is about 20%.

Tramadol is mainly metabolised by *O*- and *N*-demethylation and by conjugation reactions forming glucuronides and sulfates. Tramadol and its metabolites are mainly excreted via the kidneys. The mean elimination half-life is about 6 hours.

The *O*-demethylation of tramadol to M1, the main analgesic effective metabolite, is catalysed by cytochrome P450 (CYP) 2D6, whereas *N*-demethylation to M2 is catalysed by CYP2B6 and CYP3A4. The wide variability in the pharmacokinetic properties of tramadol can partly be ascribed to CYP polymorphism. *O*- and *N*-demethylation of tramadol as well as renal elimination are stereoselective. Pharmacokinetic-pharmacodynamic characterisation of tramadol is difficult because of differences between tramadol concentrations in plasma and at the site of action, and because of pharmacodynamic interactions between the two enantiomers of tramadol and its active metabolites.

The analgesic potency of tramadol is about 10% of that of morphine following parenteral administration. Tramadol provides postoperative pain relief comparable with that of pethidine, and the analgesic efficacy of tramadol can further be improved by combination with a non-opioid analgesic. Tramadol may prove particularly useful in patients with a risk of poor cardiopulmonary function, after surgery of the thorax or upper abdomen and when non-opioid analgesics are contraindicated.

Tramadol is an effective and well tolerated agent to reduce pain resulting from trauma, renal or biliary colic and labour, and also for the management of chronic pain of malignant or nonmalignant origin, particularly neuropathic pain. Tramadol appears to produce less constipation and dependence than equianalgesic doses of strong opioids.

Tramadol hydrochloride (tramadol), (1*RS*,2*RS*)-2-[(dimethylamino)methyl]- 1 -(3-methoxyphenyl)-cyclohexanol hydrochloride, is a centrally acting analgesic that is structurally related to codeine and morphine. It was first synthesised in 1962 and has been available for pain treatment in Germany since 1977.[1] Tramadol has a low incidence of adverse effects, particularly of respiratory depression, constipation and abuse potential,[2] and has never been a scheduled drug.[3] Therefore it became the most frequently prescribed opioid in Germany.

The registration of tramadol in the UK (1994), the US (1995) and then many other countries required extensive additional preclinical and clinical

research and increased international interest. Recent studies have confirmed the unique and unusual pharmacodynamic profile of this opioid, which is attributable to tramadol being a racemate. Both enantiomers and their metabolites contribute to the analgesic activity by means of different mechanisms.[4,5] These include binding to opioid receptors and blockade of both norepinephrine and serotonin reuptake. This duality of action has prompted the classification of tramadol by the US FDA as a nontraditional centrally acting analgesic.

1. Pharmacokinetic Properties

1.1 Pharmaceutical Formulations

Tramadol is available in various pharmaceutical forms. Ampoules contain 50mg (1mL) or 100mg (2mL) of tramadol in a solution for intravenous, intramuscular or subcutaneous injection. Immediate-release (IR) formulations, which normally require oral administration four to six times daily, are capsules (50mg), soluble tablets (50mg to be dissolved in 50mL of water), drops (50mg = 0.5mL = 20 drops or four actuations of the pump) and suppositories (100mg). Several sustained-release (SR) formulations have been developed, which provide the opportunity for administration only twice daily. SR tablets (100, 150 and 200mg) are based on a hydrophilic matrix system in which tramadol is evenly distributed. On contact with the gastrointestinal fluid, the outer layer of the tablet swells gradually and forms a retarding gel layer. SR capsules (100, 150 and 200mg) contain multiple pellets of 1mm in diameter consisting of a neutral core layered with tramadol and a membrane that controls the release. In addition, a two-phase SR tablet contains 25mg of tramadol for IR and 75mg of tramadol for SR.

1.2 Absorption

The pharmacokinetic properties of tramadol are summarised in table I. After oral administration, tramadol is absorbed almost completely and quite rapidly after a lag time of 0.2 hours for drops[6,7] and 0.5 hours for capsules.[8] Peak plasma concentrations (C_{max}) are attained within 1.2 hours after oral administration of drops[6,7] and within 1.6–1.9 hours after oral administration of capsules.[8,9] There are no available pharmacokinetic data on soluble tablets, but rapid absorption, similar to that of drops, can be expected.

Following a single oral dose of 100mg, C_{max} is approximately 300 μg/L.[6-9,11] Plasma concentration and area under the concentration-time curve (AUC) increase linearly over the dose range 50–400mg.[7,10] The extent of oral absorption of tramadol is almost 100% and the bioavailability is 70% following a single dose.[8,20-22] The difference between absorption and bioavailability is attributed to the 20–30% first-pass metabolism.[6,8,21,22] Following multiple oral administration of tramadol 100mg four times daily, C_{max} is 16% higher and AUC is 36% higher than after a single 100mg dose, indicating that oral bioavailability increases to approximately 90–100% on multiple oral administration, possibly due to saturated first-pass hepatic metabolism.[12,23] The bioavailability of drops with ethanol is about the same as that of drops without ethanol.[7] Oral administration of tramadol 100mg following a high-fat breakfast results in a 17% higher C_{max} and a 10% higher AUC than the corresponding values in fasted volunteers.[24] This increase of the bioavailability by food was not considered clinically relevant.[21,22]

After rectal administration of suppositories 100mg, tramadol absorption begins within a few minutes (0–22 minutes).[11] A C_{max} of 294 μg/L is reached within 3.3 hours.[11] The absolute bioavailability (77%) is higher than that after oral administration, probably due to a reduced first-pass metabolism after rectal administration.[11]

Tramadol is rapidly and almost completely absorbed after intramuscular injection.[17] C_{max} of 166 μg/L is reached 0.75 hours after intramuscular injection of 50mg.[17] Intramuscular injection and intravenous infusion over 30 minutes are bioequivalent with respect to the extent of systemic availability.[17] C_{max} values of 355–369 μg/L are reached 0.9 and 1.1 hours after intramuscular injections of 100mg.[18] The pharmacokinetic properties of subcutaneous tramadol, which is effective in postoperative pain,[25] have not been examined.

1.3 Sustained-Release Preparations

SR tablets and capsules provide stable plasma concentrations when administered at 12-hour inter-

Table I. Pharmacokinetic properties of tramadol

Population (n)	Route and dose (mg)	t_{max} (h)	C_{max} (μg/L)	AUC∞ (μg • h/L)	$t_{1/2\beta}$ (h)	CL (mL/min)	Reference
Volunteers (4)	PO (100)		260 (4h)	2194	5.1		10
Volunteers (4)	PO (200)		575 (3.5h)	4924	5.9		
Volunteers (3)	PO (300)		930 (4h)	8599	5.7		
Volunteers (3)	PO (400)		1220 (4.7h)	10 473	5.3		
Volunteers (10)	PO, capsules (100)	1.9	280	2488	5.1	710	8
Volunteers (8)	PO, ethanol drops (100)	1.2	308	2390	5.5	742	6
Volunteers (12)	PO, drops (50)	1.2	136	875	5.0	837	7
Volunteers (10)	PR, suppository (100)	3.3	294	2933	5.7		11
Volunteers (18)	PO (100) [single dose]	1.6	308	2549	5.6	110[a]	12
Volunteers (18)	PO (100) [qid, 1 week][b]	2.3	592	3679	6.7	73[a]	
Volunteers (12)	PO, capsules (100)	1.6	274	2177	5.9		13
Volunteers (12)	PO, SR tablets (100)	4.9	141	2119	5.7		
Volunteers (12)	PO, capsules (100) [bid, 5 days][c]	1.9	414	2970			
Volunteers (12)	PO, SR tablets (100) [bid, 5 days][d]	3.5	293	2656			
Volunteers (12)	PO, SR capsules (50)	5.3	70	1039	6.0		14
Volunteers (12)	PO, SR capsules (100)	5.9	137	2060	6.2		14
Volunteers (12)	PO, SR capsules (200)	4.9	277	3952	5.6		14
Fasting (24)	PO, SR capsules (200)	6.7	294	5293	7.2		15
Nonfasting (24)	PO, SR capsules (200)	7.0	305	5266	6.8		
Fasting (24)	PO, IR capsules (200)	2.0	640	5826	6.1		
Fasting (24)	PO, SR tablets (200)	4.5	375	5517	6.2		
Volunteers (24)	PO, IR capsules (50) [qid, 3 days]		321	5167			16
Volunteers (24)	PO, SR capsules (100) [bid, 3 days]		274	5168			
Volunteers (10)	IV (100)		409 (2h)	3709	5.2	467	8
Volunteers (8)	IV (100)		394 (2h)	3490	5.2	487	6
Volunteers (10)	IV (100)		418 (2h)	3775	5.7	447	11
Volunteers (12)	IV over 30 min (50)	0.52	287	1233	5.0	594	7
Volunteers (12)	IV over 30 min (50)	0.54	305	1332	5.5	596	17
Volunteers (12)	IM (50)	0.75	283	1353	5.5	613	
Volunteers (12)	IM (100)	0.9	355	3160			18
Volunteers (12)	IM (100)	1.1	369	3250			
65–75 years (12)	PO, capsules (100)	2.0	324	2508	6.1	793	19
>75 years (8)	PO, capsules (100)	2.1	415	3854	7.0	491	19
Renal insufficiency[e] (21)	IV (100)		894	7832	10.8	280	19
Hepatic impairment[f] (12)	PO, capsules (100)	1.9	433	7848	13.3	271	19

Continued next page

Table I. Contd

Population (n)	Route and dose (mg)	t_{max} (h)	C_{max} (µg/L)	AUC_∞ (µg • h/L)	$t_{1/2\beta}$ (h)	CL (mL/min)	Reference
Cimetidine[g] 3 days (12)	PO, capsules (100)	1.5	364	3526	7.2	521	19
Carbamazepine[h] 12 days (7)	PO, capsules (100)	1.0	150	528	2.5	3809	19

a Renal clearance.

b Multiple doses, 100mg qid for 1 week.

c Multiple doses, 100mg capsule every 12 hours for 5 days.

d Multiple doses, 100mg capsule every 12 hours for 5 days.

e Renal insufficiency with a creatinine clearance of 30–80 mL/min in five patients, 10–30 mL/min in seven patients, 5–10 mL/min in four patients and <5 mL/min in five patients.

f Alcohol-induced liver cirrhosis.

g Pretreatment with cimetidine 2 × 400mg for 3 days.

h Pretreatment with carbamazepine 2 × 400mg for 12 days.

AUC_∞ = area under the concentration-time curve from time zero to infinity; bid = twice daily; CL = total clearance; C_{max} = maximum plasma concentration; IM = intramuscular; IR = immediate-release; IV = intravenous; PO = oral; PR = rectal; qid = four times daily; SR = sustained-release; t_{max} = time to maximum plasma concentration; $t_{1/2\beta}$ = terminal elimination half-life.

vals SR tablets (100, 150 and 200mg) release 100% of the active ingredient over a 12-hour period *in vitro*.[13] The absolute bioavailability of SR tablets is 67.3% relative to the intravenous reference formulation, indicating bioequivalence of SR tablets and IR capsules (95.1%, 90% CI 87.8, 103.0%).[13] The time to C_{max} (t_{max}) of 4.9 ± 0.8 hours for the SR tablets (compared with 1.6 ± 0.5 hours for IR capsules), the C_{max} of 141.7 ± 40.4 µg/L (274.1 ± 75.3 µg/L) and the mean absorption time of 4.70 ± 0.90 hours (1.09 ± 0.56 hours) reflect the slow-release properties of the SR tablets (table I).[13]

At steady state (after 48 hours of twice-daily administration), bioavailability of the SR tablet is 87.4% (90% CI 81.3, 94.0%) relative to IR capsules administered with the same regimen.[13] The peak-trough fluctuation in plasma concentrations at steady state is reduced from 121% with the IR capsule to 66% with the SR tablet.[13] The extent of relative bioavailability of tramadol SR tablets after a lipid-rich meal (postprandial/fasting administration) is 105.1% (90% CI 99.0, 111.5%) and within the range of 80–125%.[13] Food intake has a slight influence on rate of absorption, as shown by the shorter t_{max} and higher C_{max}, indicating that food causes a slight reduction in the retarding effect.[13]

The pharmacokinetic properties of SR capsules are similar to those of SR tablets. Single doses of 50, 100 and 200mg of tramadol as SR capsules produce plasma concentrations above half of C_{max} (half-value duration) for 12.8, 12.9 and 13.0 hours, respectively.[14] There is a direct linear relationship between the administered dosage and the achieved concentration (table I).[14] Compared with with IR capsules, bioavailability is only slightly diminished, whereas C_{max} is markedly reduced and t_{max} increased (table I).[15] Compared with SR tablets 200mg, SR capsules 200mg show 95% of the AUC, 77% of the C_{max} and 118% of the half-value duration (table I), indicating enhanced retardation at almost identical bioavailability.[15] Food intake has no influence on plasma concentrations after administration of tramadol 200mg as SR capsules.[15] At steady state (reached after approximately 48 hours), the bioavailability of the SR capsule 100mg every 12 hours is 100% relative to IR capsules 50mg every 6 hours.[16] The peak-trough fluctuation in plasma

concentrations at steady state is reduced from 86% with the IR capsule to 57% with the SR capsule.[16]

The two-phase tablet of tramadol (25mg IR plus 75mg SR) produces a faster increase in plasma concentration than an IR capsule of tramadol 50mg and an SR tablet of tramadol 100mg.[26] About 2.5 hours after administration of the two-phase tablet, the concentrations become lower than those after the SR tablet of tramadol 100mg.

For subcutaneous, intramuscular or intrathecal administration, a tramadol depot system composed of monoolein and water has been developed.[27] In rats, intramuscular administration provides stable pain relief for more than 10 hours.[27] Further investigations of this novel depot system will be of interest.

1.4 Distribution

Tramadol is rapidly distributed in the body, with a distribution half-life in the initial phase of 6 minutes, followed by a slower distribution phase with a half-life of 1.7 hours.[23] The high total distribution volume of 306L after oral and 203L after parenteral administration indicates high tissue affinity; plasma protein binding is about 20%.[8,23] After intravenous injection of tramadol 100mg, plasma concentrations of 612, 553, 483 and 409 μg/L were measured after 0.25, 0.5, 1 and 2 hours.[8] In a rodent model, tramadol was particularly distributed into the lungs, spleen, liver, kidneys and brain.[21]

Brain peak concentrations of tramadol occur 10 minutes after oral administration, and those of its major active metabolite *O*-desmethyl-tramadol (M1) 20–60 minutes after oral administration.[28] In mice, the ratio tramadol/M1 in plasma was 0.5–1.0 throughout the measurements, whereas the ratio in brain was about ten at 10 minutes and about two from 20 to 50 minutes.[28] In rats, the ratio tramadol/M1 in plasma was 0.5–1.5, whereas the ratio in brain was about 15 at 10 minutes and about 4–7 thereafter.[28] There appears to be preferential brain versus plasma distribution of tramadol over M1 in mice and rats.

Tramadol passes the placental barrier, with umbilical venous plasma concentrations being 80% of maternal concentration.[29] Very small amounts (0.1%) of tramadol and M1 are excreted in breast milk, and have been detected within 16 hours after administration.[22]

1.5 Metabolism and Elimination

Tramadol is mainly excreted via the kidneys (approximately 90%); the residual activity of a radioactively labelled dose of tramadol was recovered in the faeces.[30] In a study involving nine cholecystectomised patients, only 1% of tramadol and its metabolites were eliminated via biliary excretion.[10] At 30 minutes after intramuscular administration of tramadol 50mg, tramadol concentrations in saliva and urine considerably exceeded the plasma concentration.[17] The C_{max} in saliva and urine occurred at nearly the same time as in plasma, and thereafter the plasma and saliva concentrations and the renal excretion rates decreased almost in parallel.[17] The saliva concentrations were 7- to 8-fold and the urine concentrations 43- to 46-fold higher than the corresponding plasma concentrations.[17] The mean elimination half-life is about 5–6 hours (table I).[6-12,17] The mean total clearance of tramadol was 467 mL/min (approximately 28 L/h) and 710–742 mL/min (approximately 43–44 L/h) following intravenous and oral administration, respectively.[6,8]

The main metabolic pathways of tramadol, *N*- and *O*-demethylation (phase I reactions) and conjugation of *O*-demethylated compounds (phase II reactions), were described 20 years ago.[30] Eleven metabolites were known, five arising by phase I reactions (M1 to M5) and six by phase II reactions (glucuronides and sulfates of M1, M4 and M5). Tramadol is metabolised much more rapidly in animals than in humans: 1% and 25–30% of an oral dose, respectively, are excreted unchanged in the urine.[30] In all species, M1 and M1 conjugates, M5 and M5 conjugates, and M2 are the main metabolites, whereas M3, M4 and M4 conjugates are only formed in minor quantities (table II).[30] In a study where a 50mg oral dose of tramadol was given to 104 volunteers, mean values for tramadol, M1 and M2 excretion in 24-hour urine were 12%, 15% and 4% of the administered dose, respectively.[31] However, great interindividual differences were observed in two humans after oral administration of either 1.06 or 1.25 mg/kg of ^{14}C-labelled tramadol.[30] One volunteer produced mainly M1, M5, M1 conjugates and M5 conjugates, whereas the other produced

Table II. Excretion of unchanged tramadol and its metabolites in the urine of humans, dogs and rats receiving oral tramadol, and metabolites found in human hepatic microsomes[2431,3234]

Analyte	Chemical structure[2431,3234]	Percentage of each analyte found								
		human[a]	human[b]	dog[c]	rat[d]	human[e]	human[f]	hepatic[g]	rat[h]	dog[i]
Tramadol		25	32	1	0.9	12	>10	82	2	2
M1	*O*-Desmethyl-tramadol	10	5	2	9	15	>10	5	13	6
M2	*N*-Desmethyl-tramadol	2	31	5	17	4	>10	6	13	6
M3	*N,N*-Didesmethyl-tramadol	ND	0.8	2	10		5–10	ND	9	4
M4	*O,N,N*-Tridesmethyl-tramadol	0.1	0.8	4	2		<2	<0.5	<2	<2
M5	*O,N*-Didesmethyl-tramadol	13	6	10	14		5–10	<0.5	5	6
M6	4-Hydroxycyclohexyl-tramadol						2–5	3	<2	3
M7	4-Hydroxycyclohexyl-*N*-desmethyl-tramadol						<2	ND	<2	3
M8	4-Hydroxycyclohexyl-*N,N*-didesmethyl-tramadol						<2	ND	<2	<2
M9	4-Oxocyclohexyl-tramadol						<2	ND	<2	<2
M10	Dehydrated tramadol						<2	ND	<2	<2
M11	2-Formyl-1-[3-methoxyphenyl]cyclohexanol						<2	ND	<2	<2
M12	Tramadol glucuronide						<2	ND		
M13	M1 glucuronide						2–5	ND	7	<2
M14	M4 glucuronide						<2	ND	<2	<2
M15	M5 glucuronide						2–5	ND	10	7
M16	M6 glucuronide						2–5	ND	<2	8
M17	M7 glucuronide						<2	ND	<2	7
M18	M8 glucuronide						<2	ND	ND	<2
M19	Tramadol sulfate						<2	ND		
M20	M1 sulfate						2–5	ND		
M21	M4 sulfate						2–5	ND		
M22	M5 sulfate						5–10	ND		
M23	M6 sulfate						<2	ND		
M24	M7 sulfate								ND	<2
M25	Acetyl-M2								<2	<2
M26	Dehydro-M3								<2	<2
M27	Dehydro-M11								<2	<2
M28	Alcoholic metabolite								<2	<2
M29	Carboxylic acid								<2	<2
M30	M29 glucuronide								ND	<2
M31	Tramadol N-oxide						ND	2	ND	ND

Continued next page

Table II. Contd

Analyte	Chemical structure[30,33,34]	Percentage of each analyte found							
		human[a]	human[b]	dog[c]	rat[d]	human[e]	human[f]	hepatic[g]	rat[h]	dog[i]
M32	Hydroxy-M1						ND	<1	ND	ND
M33	Dehydrated M31						ND	<2		
M13 or M20	M1 conjugates	15	8	12	11					
M14 or M21	M4 conjugates	0.8	0.2	6	4					
M15 or M22	M5 conjugates	15	6	33	14					
	Unknown	18	11	25	20					

a Urine (0–72h) of humans (n = 1) after oral tramadol 1.25 mg/kg.[30]
b Urine (0–72h) of humans (n = 1) after oral tramadol 1.06 mg/kg.[30]
c Urine (0–72h) of dogs (n = 3) after oral tramadol 10.5 mg/kg.[30]
d Urine (0–72h) of rats (n = 5) after oral tramadol 30 mg/kg.[34]
e Urine (0–24h) of humans (n = 104) after oral tramadol 50mg.[31]
f Urine (4–12h) of humans (n = 3) after oral tramadol 100mg.[33]
g Human liver microsomal fraction incubated with tramadol 10 mg/L.[33]
h Urine (0–24h) of rats (n = 4) after oral tramadol 50 mg/kg.[34]
i Urine (0–24h) of dogs (n = 2) after oral tramadol 20 mg/kg.[34]
ND = not detected.

mainly M2 (table II).[30] In contrast to the above-mentioned studies involving Caucasians, the biotransformation of tramadol appears to be remarkably reduced in African subjects.[32] In 10 Nigerian volunteers, about 96% of tramadol was excreted unchanged in the urine after oral administration of 100mg.[32] There is a need to investigate racial variations in the metabolism of tramadol in more detail.

In a recent study, a total of 23 metabolites, consisting of 11 phase I metabolites (M1 to M11) and 12 conjugates (seven glucuronides, five sulfates), were profiled in the urine of male volunteers after oral tramadol 100mg.[33] These metabolites were formed via the following six metabolic pathways: *O*-demethylation, *N*-demethylation, cyclohexyl oxidation, oxidative *N*-dealkylation, dehydration and conjugation.[33] The previously known metabolites (M1 to M5)[30] were confirmed as major metabolic products (table II). Six additional phase I metabolites (M6 to M11) resulted from newly identified pathways and had not previously been reported. M12 to M18 were identified as glucuronides and M19 to M23 as sulfates, of which M13 to M15 and M20 to M23 had previously been reported as M1, M4 and M5 conjugates.[30] Additional phase I metabolites (M25 to M29) and phase II metabolites (M24 and M30) have been identified in rats or dogs, but not in humans (table II).[33,34]

The *in vitro* metabolism of tramadol has been studied in a human liver microsomal fraction incubated with tramadol 10 mg/L.[33] Unchanged tramadol (82% of the sample) plus eight metabolites (M1, M2, M4, M5 and M6, plus M31, M32 and M33, which were not found in urine) were identified (table II).[33] Of the 26 identified metabolites in humans, seven (M12, M19 to M23 and M33) have not been found in the rat or dog.[34]

The metabolism of tramadol to M1 is slow in humans (table III). After oral or rectal administration of tramadol 100mg, the t_{max} of M1 is about 1.4 hours longer than that of tramadol and the C_{max} of M1 is no more than 18–26% of that of tramadol.[12,35] After multiple oral doses or administration of SR capsules, the time to reach C_{max} of tramadol and M1 was similar.[12,36] After single and multiple oral administration of tramadol, the AUC for M1 was about 25% of that of the parent com-

Table III. Pharmacokinetic properties of M1 and tramadol after administration of tramadol

Study	Population (n)	Administration	Analyte	t_{max} (h)	C_{max} (µg/L)	AUC_∞ (µg • h/L)	$t_{1/2\beta}$ (h)	CL (mL/min)
Liao et al.[74]	Volunteers (16)	PO, 100mg (single dose)	Tramadol	1.6	308	2649	5.6	110[a]
			M1	3.0	55	722	6.7	186[a]
		PO, 100mg (qid, 1 week)[b]	Tramadol	2.3	592	3679	6.7	73[a]
			M1	2.4	110	835	7.0	134[a]
Thuraul et al.[96]	Volunteers (20)	PO (SR capsules), 100mg	Tramadol	4.8	160	1402[c]		
			M1	4.7	73	618[c]		
		PO (SR capsules), 200mg	Tramadol	4.4	295	2598[c]		
			M1	5.4	143	1201[c]		
Nobilis et al.[33]	Volunteers (24)	PR (suppositories)[c], 100mg	Tramadol	2.5	796[d]	9510[f]	9.1	
			M1	4.0	214[d]	3590[f]		
		PR (suppositories)[d], 100mg	Tramadol	2.7	873[d]	10 410[f]	8.5	
			M1	4.0	230[d]	3960[f]		
Murthy et al.[97]	Children (9)	IV, 2 mg/kg	Tramadol	0.19	1079	5738	6.4	6.1[g]
			M1	4.9	64	1172	10.6	
	Children (5)	Caudally, 2 mg/kg	Tramadol	0.55	709	4774	3.7	6.6[g]
			M1	6.4	40	556	5.4	

a Renal clearance.

b Multiple doses, 100mg qid for 1 week.

c AUC_{12}.

d Two different pharmaceutical formulations.

e nmol/L.

f AUC_{∞} (µmol • h/L).

g mL/min/kg.

AUC_∞ = area under the concentration-time curve from time zero to x hours; AUC_∞ = area under the concentration-time curve from time zero to infinity; C_{max} = maximum plasma concentration; CL = total clearance; IV = intravenous; PO = oral; PR = rectal; qid = four times daily; SR = sustained-release; t_{max} = time to maximum plasma concentration; $t_{1/2\beta}$ = terminal elimination half-life.

pound and the elimination half-life of M1 was 6.7 and 7.0 hours, respectively, which is not substantially different from that of tramadol.[12]

The pharmacokinetic properties of other metabolites have not been investigated in detail. It has been reported that the biological half-lives of the metabolites are similar to that of the parent substance, diminishing the likelihood of accumulation of metabolites after multiple administration.[23] Like tramadol, all metabolites are almost completely excreted via the kidneys; from a quantitative point of view, biliary excretion of these components is negligible.[30]

The *N*-oxide of tramadol is a prodrug for tramadol.[38] Although tramadol *N*-oxide has no direct pharmacodynamic effects, it produces dose-related long-lasting antinociception in the mouse and rat.[39] Tramadol concentrations were essentially the same after administration of either tramadol or tramadol *N*-oxide to mice, suggesting complete conversion.[39] In contrast to the rapid attainment of C_{max} and rapid decline in tramadol plasma concentration after tramadol administration, tramadol concentrations increase more gradually and were maintained for a longer period after administration of tramadol *N*-oxide.[39] Therefore, tramadol *N*-oxide could offer the clinical benefits of an extended duration of action and a 'blunted' plasma concentration spike, possibly leading to an improved adverse effect profile.[39]

1.6 Influence of Cytochrome P450 on Biotransformation

In vitro investigations suggest that the *O*-demethylation of tramadol to metabolite M1 is catalysed by the liver enzyme cytochrome P450 (CYP) 2D6, because this biotransformation is inhibited by quinidine, a selective CYP2D6 inhibitor.[40,41] In addition, good correlations were obtained between M1 formation and dextromethorphan *O*-demethylase, a marker for CYP2D6, in human liver microsome preparations.[41] The gene encoding for CYP2D6 is known to show polymorphism and the existence of different alleles results in functionally different enzymes.[42] Phenotypically, 90–95% of Caucasians are 'extensive metabolisers' and the remainder are 'poor metabolisers' of CYP2D6 probe substrates such as debrisoquine and sparteine.

M1 production in microsomes prepared from the liver of a poor metaboliser was markedly reduced.[43] After administration of tramadol 2 mg/kg, the plasma concentration of (+)-M1 ranged from 10 to 100 μg/L in extensive metabolisers, whereas in poor metabolisers plasma concentrations of (+)-M1 were below or around the detection limit of 3 μg/L.[44] Furthermore, poor metabolisers had inferior analgesic effects, because tramadol interacts with μ opioid receptors predominantly by way of M1.[44]

In a study of 104 healthy volunteers, poor metabolisers of sparteine exhibited a 5-fold higher tramadol/M1 plasma concentration ratio than extensive metabolisers.[31] Furthermore, there was a highly significant correlation between sparteine oxidation and tramadol *O*-demethylation in extensive metabolisers.[31]

However, the biotransformation of tramadol varies within the phenotypic population of extensive metabolisers depending on the genotype of CYP2D6.[45] In 13 children, there was only a modest correlation between tramadol/M1 plasma concentration ratio and CYP2D6 activity, as determined by dextromethorphan urinary metabolite ratio; however, when subjects were segregated based on the number of functional CYP2D6 alleles, a much stronger relationship was observed for subjects with two functional alleles, with essentially no relationship evident in those individuals with one functional allele.[45] Further evaluation of these data suggested that the CYP2D6-mediated metabolite (M1) is formed to a lesser extent, and the formation of the non-CYP2D6 product (M2) is more pronounced, in subjects with one versus two functional alleles.[45]

The importance of the CYP2D6 genotype for the biotransformation of tramadol has been emphasised by a study in Malaysian subjects.[46] Compared with 5–10% of Caucasians, only 1% of Asians are homozygous for mutant CYP2D6 alleles such as CYP2D6*3, *4 or *5, which results in no functional protein being formed.[46] Despite this low frequency of poor metabolisers in the Asian population, they carry a high frequency (51%) of the CYP2D6*10 allele, which is relatively rare in Caucasian populations.[46] This mutation leads to an unstable enzyme with lower metabolic activity. Of 30 healthy Malaysians, all being extensive metabolisers, those who were homozygous for CYP2D6*10 had a longer

plasma half-life of tramadol than subjects in the heterozygous or normal groups (7.2, 10.0 and 12.1 hours, respectively) [46] When these patients were screened for the presence of other alleles as well, the pharmacokinetic parameters were even better explained: tramadol half-lives were 6.6 hours for CYP2D6*1/*1, 7.4 hours for CYP2D6*1/*9 and CYP2D6*1/*10, 7.5 hours for CYP2D6*1/*4 and CYP2D6*1/*5, 8.5 hours for CYP2D6*10/*10 and CYP2D6*10/*17 and 21.5 hours for CYP2D6*4/*10 and CYP2D6*5/*10.[46]

Investigations in human liver microsomes have shown differences between the kinetics of *O*- and *N*-demethylation [41] Although M1 is the major metabolite formed at low tramadol substrate concentrations, M2 formation predominates at high substrate concentrations [41] The biphasic kinetics of both M1 and M2 formation indicate the participation of more than one CYP isoform in these pathways of tramadol metabolism [41] In the presence of low CYP2D6 concentrations or when the *O*-demethylation of tramadol is inhibited, a metabolic switch in favour of enhanced *N*-demethylation can be observed.[22,47] *In vivo*, however, there was no correlation between CYP2D6 activity, determined by sparteine oxidation, and tramadol *N*-demethylation.[31]

In vitro, the *N*-demethylation of tramadol to metabolite M2 is catalysed by cDNA-expressed human CYP2B6 and CYP3A4.[41] In addition, M2 formation was inhibited by the CYP3A4 inhibitor troleandomycin to 33–44% of control, and good correlations were obtained between M2 formation and (*S*)-mephenytoin *N*-demethylase, a marker for CYP2B6, in human liver microsomes [41]

Based on the observations that CYP2D6 primarily catalyses tramadol *O*-demethylation (M1 formation), whereas CYP2B6 and CYP3A4 primarily catalyse tramadol *N*-demethylation (M2 formation), CYP2D6 would be expected to participate in M5 formation from M2.[41] In addition, CYP2B6 and CYP3A4 would be expected to participate in M1 metabolism to M5, and M2 metabolism to M3 [41] Additional studies, using M1 and M2 as substrates, are required to fully elucidate the CYP isoforms involved in M3 and M5 formation Further *in vitro* and *in vivo* studies should investigate the influence of CYP isoforms on the formation of the remaining tramadol metabolites

The wide variability in the pharmacokinetic properties of tramadol can partly be ascribed to CYP polymorphism. Because fluctuations in the concentrations of tramadol and its pharmacodynamically active metabolites have impact on the therapeutic response and toxicity of tramadol, genotypic and phenotypic characterisation of individuals and populations becomes increasingly important to predict enzyme activity, individualise drug therapy and thus maximise safety and efficacy.

1.7 Stereoselective Pharmacokinetic Properties

Tramadol is administered as a racemic mixture of two enantiomers, (+)-tramadol and (−)-tramadol, that are essentially metabolised by the liver producing (+)-metabolites and (−)-metabolites, respectively Several *in vitro* and *in vivo* studies have shown that the metabolism and distribution of tramadol are stereoselective. So far, no study has investigated whether interconversion of the enantiomers of tramadol or its metabolites occurs.

In vitro, *O*- and *N*-demethylation of tramadol were both demonstrated to be stereoselective [40] The *O*-demethylation of tramadol, leading to M1, was determined to be 2-fold greater for the (−)-enantiomer than for the (+)-enantiomer [40] On the other hand, *N*-demethylation, leading to M2, was considerably faster after incubation of the (+)-enantiomer compared with the (−)-enantiomer [40] Since *O*-demethylation is the preferred biotransformation of tramadol in most subjects, higher plasma concentrations of (+)-tramadol and (−)-M1 compared with (−)-tramadol and (+)-M1, respectively, can be expected *in vivo*.

To study the stereoselectivity of renal clearance, isolated kidneys of rats were perfused with tramadol and M1.[48] The renal clearance of the enantiomers of both compounds was stereoselective, (−)-tramadol and (+)-M1 being preferentially eliminated In addition, the *O*-demethylation of tramadol was stereoselective in the kidneys, (−)-tramadol being preferentially metabolised.[48]

The distribution of tramadol in the central nervous system of rats is also stereoselective [49] At 1 hour after intraperitoneal administration of tramadol 17 mg/kg, concentrations of (+)-tramadol were

Table IV. Stereoselective pharmacokinetic properties of tramadol and M1 after administration of tramadol

Reference	Population (n)	Administration	Analyte	t_{max} (h)	C_{max} (µg/L)	AUC_∞ (µg • h/L)	$t_{1/2\beta}$ (h)	CL (mL/min)
Campanero et al.[48]	Volunteers (12)	IV over 30 min, 100mg	(+)-Tramadol			1815	5.5	423[a]
			(−)-Tramadol			1348	4.6	554[a]
			(+)-M1			515	9.1	1513[a]
			(−)-M1			501	9.0	1500[a]
Ceccato et al.[52]	Volunteers (30)	PO, 100mg	(+)-Tramadol	1.8	323	2784[b]		
			(−)-Tramadol	1.8	290	2227[b]		
			(+)-M1	2.1	61	697[b]		
			(−)-M1	2.1	61	761[b]		
Liu et al.[54]	Volunteers (12)	PO (SR tablets), 100mg (bid, 5 days)	(+)-Tramadol	4.2	164	2482	7.8	
			(−)-Tramadol	3.4	144	1911	6.2	
			(+)-M1	3.8	18	162		
			(−)-M1	3.4	23	179		

a mL/h/kg.

b AUC_{ss}.

AUC_{ss} = area under the concentration-time curve from time zero to 36 hours; AUC_∞ = area under the concentration-time curve from time zero to infinity; bid = twice daily; CL = total clearance; C_{max} = maximum plasma concentration; IV = intravenous; PO = oral; SR = sustained-release; t_{max} = time to maximum plasma concentration; $t_{1/2\beta}$ = terminal elimination half-life.

higher than those of (−)-tramadol and concentrations of (−)-M1 were higher than those of (+)-M1 in plasma, cerebrospinal fluid and cerebral cortex.[49] Tramadol and M1 concentrations of both enantiomers were the highest in cerebral cortex and the lowest in cerebrospinal fluid.[49] At 1 hour after intraperitoneal administration of M1 5 mg/kg, the concentrations of (+)-M1 were higher than those of (−)-M1 in plasma, cerebrospinal fluid and cerebral cortex, which was different from the results after intraperitoneal administration of tramadol.[49] The concentrations of both enantiomers of M1 were the highest in cerebral cortex and the lowest in cerebrospinal fluid.[49] Following intravenous infusion of (+)-M1 or (−)-M1 in rats, the pharmacokinetics of both substrates were similar and could best be described by a two-compartment model.[50] There was no pharmacokinetic interaction between the two compounds.[51]

Following an intravenous infusion of tramadol 100mg over 10 minutes to 12 human volunteers, at all times of the observation period (10 minutes to 24 hours) plasma concentrations, AUC and elimination half-life of (+)-tramadol were greater than those of (−)-tramadol (table IV).[52] On the other hand, (+)-M1 concentrations were lower than (−)-M1 concentrations between 10 minutes and 8 hours after infusion, but greater at 12 and 24 hours.[52]

After oral administration of tramadol 200mg, t_{max} was identical for (+)-tramadol and (−)-tramadol, as well as for (+)-M1 and (−)-M1 (table IV).[53] The C_{max} and AUC values of (+)-tramadol were greater than those for (−)-tramadol, and those of (−)-M1 were greater than those of (+)-M1 (table IV).[53] Another study investigated the stereoselective pharmacokinetics of tramadol after multiple oral doses of SR tablets 100mg.[54] (+)-Tramadol was shown to be absorbed more completely, but eliminated more slowly. At steady state, the plasma concentrations of (+)-tramadol were higher than those of (−)-tramadol at every sampling timepoint, and those of (−)-M1 were higher than those of (+)-M1 at most sampling timepoints. A time-dependent increase of the (+)/(−)-tramadol ratio and the (−)/(+)-M1 ratio was observed during the 32-hour sampling period. Although the (+)/(−)-tramadol ratios were similar among the 12 subjects (range 1.19–1.48), the (−)/(+)-M1 ratios were very different (range

0.89–1.90). It needs to be determined whether the pharmacokinetic stereoselectivity of the enantiomers of M1 is caused by different levels of protein binding, different rates of renal clearance and/or polymorphism of CYP2D6.

Analysis of the enantiomers of tramadol and its metabolites in the urine of volunteers has confirmed that a stereoselective metabolism of tramadol clearly occurs. After oral administration of tramadol 100mg, 16% of the dose was excreted within 30 hours in the urine as unchanged tramadol, 16% as M1, 2% as M2 and 15% as M5.[55] For all compounds, a time-dependent increase of the initial enantiomeric ratio was observed during the study period.[55] The enantiomeric ratios [(+)/(−) for tramadol; not determined if (+)/(−) or (−)/(+) for metabolites] were 1.22 for tramadol, 1.48 for M1, 2.29 for M2 and 2.19 for M5.[55] This is in good agreement with the results of other investigations, which also showed a higher excretion of the (+)-enantiomer.[56-58] In addition, a 4- to 5-fold higher excretion of the (−)-enantiomers of two phase II metabolites, *O*-demethyl-tramadol glucuronide (M13) and *N,O*-didemethyl-tramadol (M15), was observed after oral administration of tramadol 100 or 150mg to volunteers.[58,59]

1.8 Pharmacokinetic-Pharmacodynamic Modelling

Pharmacokinetic-pharmacodynamic studies are used to describe and predict the time course of the *in vivo* effect in different scenarios. For tramadol, interpretation of the pharmacokinetic-pharmacodynamic relationship is difficult because of: (i) a delay of effect resulting from transport from plasma to central nervous system; (ii) potential development of tolerance; and (iii) pharmacodynamic interactions among the two enantiomers of tramadol and its active metabolites.[50] So far, only two animal studies have investigated the pharmacokinetic-pharmacodynamic relationships of tramadol.[50,51]

The first pharmacokinetic-pharmacodynamic study investigated the pharmacokinetic properties and the antinociceptive and respiratory effects of the two main metabolites of tramadol, (+)-M1 and (−)-M1, in rats.[50] The pharmacokinetics of both compounds were considered similar and were well described with multicompartment models. (+)-M1 2 mg/kg was enough to achieve 100% antinociception without respiratory depression. Antinociceptive response elicited by (+)-M1 could be adequately described by a standard pharmacokinetic-pharmacodynamic model. In addition, the results indicated the development of tolerance for the antinociceptive effects of (+)-M1. The administration of doses of (+)-M1 higher than 2.5 mg/kg elicited dose-dependent respiratory depression. However, doses of (−)-M1 up to 8 mg/kg showed neither antinociception nor respiratory effects.[50]

The second pharmacokinetic-pharmacodynamic study investigated the interactions between (+)-M1 and (−)-M1 in rats.[51] The pharmacokinetic parameters of both enantiomers infused together were similar to those obtained when both compounds were administered alone; no pharmacokinetic interaction between (+)- and (−)-M1 was found. Although (−)-M1 alone showed no antinociception,[50] it caused potentiation of the antinociceptive effect elicited by (+)-M1. This phenomenon has successfully been modelled by using a noncompetitive interaction model, including an effect compartment to account for the opioid effect of (+)-M1 and an indirect response model accounting for the release of norepinephrine by (+)-M1 and inhibition of norepinephrine reuptake by (−)-M1.[51,60]

In humans, no pharmacokinetic-pharmacodynamic modelling has been performed so far. Two studies investigated the analgesic effect of SR tramadol in 20 volunteers with an experimental pain model.[36,61] In both studies, the antinociceptive effects did not correlate with changes in pharmacokinetics. The authors concluded that these discrepancies might be based on differences between tramadol concentrations in plasma and at the site of action.

Another approach was the determination of 'minimum effective' plasma concentrations during intravenous patient-controlled analgesia (PCA) for postoperative pain. Venous blood samples were taken immediately before a patient's demand, i.e. at the point in time at which the patient was just becoming dissatisfied with analgesia.[62-64] The determined mean minimum effective concentrations varied depending on the study conditions, and were 298 μg/L in a study where patients received at least 5 μg/kg fentanyl intraoperatively,[64] 590 μg/L in a study

where patients received no opioids whatsoever besides tramadol[62] and 916 μg/L in a study where tramadol PCA was combined with a continuous infusion of tramadol at 12 mg/h independent of the demands.[63] The range of minimum effective concentrations was rather broad in all of these three studies – 20–986 μg/L,[64] 65–2169 μg/L[62] and 272–1900 μg/L.[63] The relative parenteral opioid potency derived from minimum effective concentrations in postoperative pain treatment was calculated to be 0.05 : 1 for tramadol compared with morphine.[65]

The minimum effective concentrations of M1 (84 and 36 μg/L) were only 12–14% of those of tramadol.[62,64] Plasma concentrations did not rise from the initial to the final blood sample (tramadol, 250 vs 208 μg/L; M1, 30 vs 34 μg/L),[65] indicating that accumulation or acute tolerance does not develop during short postoperative use of tramadol.

During intravenous PCA using (+)-tramadol, tramadol racemate and (−)-tramadol, the mean plasma concentrations of tramadol were 470, 590 and 771 μg/L, and those of M1 were 57, 84 and 96 μg/L, respectively.[62] The finding that the minimum effective concentrations of tramadol and M1 in the (+)-tramadol group were lower than those in the (−)-tramadol group confirms that (+)-tramadol or (+)-M1 are more potent analgesics than the (−)-enantiomers.[62] Stereoselective analysis showed that the concentrations of (+)-tramadol and (+)-M1 were lower in the tramadol racemate group than in the (+)-tramadol group; this finding suggests that a potentiation in the analgesic effect elicited by (+)-tramadol or (+)-M1 is caused by (−)-tramadol or (−)-M1 in humans.[62]

The concentrations described as 'minimum effective' in these studies,[62-64] however, are not really 'minimum effective' because no quantitative data are available for the roles of tramadol, M1 and other metabolites in the analgesic effect of tramadol.[62] In addition, all studies demonstrated a great inter- and intraindividual variability in postoperative plasma concentrations and could not fix narrow analgesic threshold concentrations.[62]

Proper pharmacokinetic-pharmacodynamic characterisation of tramadol in humans, which implies the administration of (+)-tramadol, (−)-tramadol, (+)-M1 and/or (−)-M1 and use of enantioselective analytical methods to quantify plasma concentrations of each of the important and active components, is required to allow better understanding of tramadol effects.

1.9 Effect of Age and Impaired Renal and Hepatic Function

The pharmacokinetics of tramadol are not age-dependent (table I). Only one study has investigated the pharmacokinetic properties of tramadol in children (table I).[37] After intravenous injection of tramadol 2 mg/kg in nine children aged 1–7 (median 2.4) years, the mean plasma concentrations of tramadol and M1 were only slightly higher than those in adults.[37] None of the pharmacokinetic variables calculated was significantly different from those in healthy adult volunteers.[37] As *O*-demethylation of tramadol is carried out by CYP, which usually reaches adult levels by 1 year of age, it is not surprising that the M1/tramadol plasma concentration ratio after intravenous injection was similar to that in adults.[37] The AUC value in five children aged 6–12 (median 6.0) years after caudal administration was only 17% lower than after intravenous injection, demonstrating that there is extensive systemic absorption of tramadol after caudal administration.[37]

Only one study has investigated the pharmacokinetic properties of tramadol in older subjects (table I).[19] There were no clinically relevant differences in pharmacokinetic properties between healthy adult volunteers aged <65 years and volunteers aged >65–75 years. However, elimination may be prolonged in patients >75 years of age.[19]

Since tramadol and its main pharmacologically active metabolite M1 are eliminated both metabolically and renally, the terminal half-life may be prolonged in hepatic or renal function disorders. However, the prolongation of the elimination half-life is relatively slight, as long as one of the two excretion organs is virtually intact.[19] In patients with severe liver cirrhosis, the elimination half-life of tramadol was extended to a mean of about 13 hours; extreme values reached up to 22 hours.[19] In addition, the renal clearance of unchanged tramadol increases in patients with liver cirrhosis.[66] Since it is not yet known whether patients with liver cirrhosis experience sufficient pain relief after recommended doses

of tramadol, and because of the potential for delayed elimination and accumulation, it appears advisable to consider alternative drugs in this setting until more information becomes available.[66]

In patients with renal failure whose creatinine clearance was <5 mL/min the mean elimination half-life of tramadol was about 11 hours; extreme values reached about 19 hours.[19] The administration of tramadol 50mg four times daily on a haemodialysis-free day resulted in a t_{max} of 3 hours and an elimination half-life of 6.4 hours, both being comparable to those in healthy subjects.[67] However, total clearance (151 mL/min) and volume of distribution (83L) were decreased, and thus the C_{max} increased (478 µg/L).[67] Therefore, the doses and intervals of tramadol should be adjusted in patients with severe renal impairment.

Dialysis appears not to have a significant effect on tramadol concentrations. The total amount of tramadol and M1 removed during a 4-hour dialysis period (haemodialysis, intermittent or continuous haemofiltration, peritoneal dialysis) was <7% of the administered dose.[10] However, a case report described a 55% extraction ratio during haemodialysis and recommended that tramadol administration should be performed after the session of haemodialysis.[67]

1.10 Drug Interactions

An interaction study with cimetidine, a typical enzyme inhibitor, showed that previous administration of cimetidine 400mg twice daily for 3 days resulted in an increase of tramadol AUC (27%) and elimination half-life (20%),[19] an effect that was not considered to require dosage adjustment.[10]

Investigations on the interaction with carbamazepine 400mg twice daily for 12 days as a typical enzyme inducer showed that tramadol C_{max} (51%), AUC (26%) and elimination half-life (54%) were reduced.[19] Therefore, an increase in tramadol dosage should be considered in patients with previous or concomitant carbamazepine treatment.

There is no interaction between tramadol and coumarin anticoagulants.[68]

2. Pharmacodynamic Properties

2.1 Mechanism of Action

Tramadol has a weak affinity for the µ opioid receptor. A second, non-opioid, mechanism is suggested by: (i) lack of naloxone reversibility; (ii) lack of significant naloxone-induced withdrawal; (iii) production of mydriasis (rather than miosis); and (iv) attenuation of its antinociceptive or analgesic effect by non-opioid (i.e. serotonin or adrenergic) antagonists.[69]

Tramadol possesses only a modest affinity for µ opioid receptors and no affinity for δ or κ opioid receptors.[4] The affinity of tramadol for µ opioid receptors is approximately 10-fold less than that of codeine and 6000-fold less than that of morphine, an affinity that by itself does not seem sufficient to contribute to the analgesic action of tramadol (table V). The metabolite M1 binds with about 300-fold higher affinity than the parent compound, but still with much lower affinity than morphine.[60,70,71] The increase in subjective and objective pain thresholds induced by tramadol is, in contrast to that of other opioids, only partially blocked by the opioid antagonist naloxone.[72] Therefore, the activation of µ

Table V. Relative activity for inhibition of opioid receptor binding or monoamine uptake[6,73]

Drug	K_i (µmol/L)				
	opioid receptor affinity			uptake inhibition	
	µ	δ	κ	norepinephrine	serotonin
(±)-Tramadol	2.1	57.6	42.7	0.78	0.9
(+)-Tramadol	1.3	62.4	54.0	2.51	0.53
(−)-Tramadol	24.8	213	53.5	0.43	2.35
(+)-M1	0.00034				
Morphine	0.00034	0.092	0.57	IA	IA
Imipramine	3.7	12.7	1.8	0.0066	0.021

IA = inactive; K_i = inhibition constant.

opioid receptors appears to be only one of the components of the mechanism of action of tramadol.

In addition to its opioid actions, tramadol inhibits the neuronal reuptake of norepinephrine and serotonin (5-hydroxytryptamine, 5-HT).[4] These monoamine neurotransmitters are involved in the antinociceptive effects of descending inhibitory pathways in the central nervous system. The α_2-adrenoceptor antagonist yohimbine and the serotonin antagonist ritanserin block the antinociceptive effects of tramadol,[72] but not those of morphine.[4] The reuptake inhibition of the non-opioid system requires the same range of concentrations as the inhibition of the opioid system (table V), suggesting that both mechanisms are active *in vivo*.

Tramadol is a racemate of 50% (+)-enantiomer and 50% (−)-enantiomer.[74] (+)-Tramadol has a 2-fold higher affinity for the μ opioid receptor than the racemate (table V).[5] Of the metabolites, (+)-M1 has the highest affinity for the μ opioid receptor, being about 700-fold more potent than (±)-tramadol.[73] Another metabolite with a higher affinity than (±)-tramadol for the μ opioid receptor is (±)-M5.[73] The intravenous administration of M1, but not of M5, produced strong antinociceptive effects.[71] However, a pronounced effect was seen after direct administration of M5 into the brain ventricle, indicating that M5 does not penetrate the blood-brain barrier because of its high polarity.[71] Therefore *in vivo*, (+)-M1 appears to be responsible for the μ opioid-derived analgesic effect of tramadol.

(±)-Tramadol inhibits the neuronal reuptake of serotonin; the (+)-enantiomer is about 4-fold more potent than the (−)-enantiomer.[75] In addition, (±)-tramadol and its (+)-enantiomer, but not the (−)-enantiomer and M1, increase serotonin efflux.[76] Whereas one study suggests that an enhancement of serotonin release contributes to its actions,[77] another study indicates that tramadol is only a serotonin reuptake blocker and not a serotonin releaser.[78] Furthermore, the serotonergic pathway is responsible for the antinociceptive effect of tramadol in the formalin test, and this effect is mediated by 5-HT_2 receptors.[79]

Tramadol enhances extraneuronal norepinephrine levels in the spinal cord by competitive interference with the norepinephrine reuptake mechanism.[80] The site of interference is the norepinephrine transporter function.[81] The effect on norepinephrine efflux was smaller than the effect on norepinephrine uptake.[82] (−)-Tramadol is a more potent blocker of norepinephrine reuptake than is (+)-tramadol or M1.[82,83]

These findings led to the hypothesis that tramadol produces its antinociception in animals and analgesia in humans by a multimodal mechanism.[69] (+)-M1 acts as a μ opioid agonist, (+)-tramadol inhibits serotonin reuptake and (−)-tramadol inhibits norepinephrine reuptake. The activity of the individual enantiomers at either the opioid or monoamine uptake sites is low when compared with such reference compounds as morphine for the opioid sites and imipramine for the uptake sites (table V).[69]

In rats, the measured effective dose to produce 50% antinociception (ED_{50}) of racemic tramadol was lower than the theoretical value calculated if the contributions of the enantiomers were simply additive.[5] Thus, combined as a racemate, the enantiomers of tramadol act in a synergistic manner and are more efficacious. It is of great interest that less-than-synergistic interactions have been observed for adverse events, i.e. in the rotarod test and the colonic propulsive motility test.[5] The severity of adverse events seen with the racemate is reduced because these effects predominate with one or the other of the enantiomers and, in part, they antagonise each other.

2.2 Analgesic Effects

In healthy volunteers undergoing experimental pain, oral tramadol 100mg and intravenous tramadol 2 mg/kg provided analgesia superior to that of placebo.[84,85] Analgesia peaked at 3 hours and lasted for about 6 hours.[84] Tramadol-induced analgesia was only partly antagonised by the opioid antagonist naloxone.[84,86] The combination of naloxone and the α_2-adrenoceptor antagonist yohimbine abolished the analgesic effects of tramadol.[72] Furthermore, ondansetron, a selective $5HT_3$ receptor antagonist, reduced the analgesic effects of tramadol in postoperative pain.[87,88] These data point to the synergy of monoaminergic modulation and opioid agonism in tramadol-induced analgesia in humans.

Tramadol interacts with μ opioid receptors predominantly by way of its metabolite (+)-M1.[44] In

extensive sparteine metabolisers, the analgesic effects of tramadol were superior to those in poor metabolisers [44] Therefore, the formation of (+)-M1 by CYP2D6 is important for the analgesic effect of tramadol.

Three studies investigated the extent of analgesia contributed by the enantiomers of tramadol in humans.[89-91] In healthy volunteers, oral (+)-tramadol was associated with an immediate rapid increase in the pain threshold that could be inhibited by naloxone [91] (−)-Tramadol and the racemate both induced antinociceptive effects of a similar magnitude that were not affected by naloxone [91] Following orthopaedic surgery, intravenous administration of up to 150mg of (+)-tramadol, (−)-tramadol or the racemate were superior to placebo, but inferior to morphine (up to 15mg).[90] Whereas (+)-tramadol and morphine had the highest rate of adverse events, tramadol racemate had the lowest rate.[90] In a randomised double-blind study, 98 patients recovering from major gynaecological surgery were treated with intravenous PCA.[89] Of patients treated with (+)-tramadol, racemate or (−)-tramadol, 67%, 48% and 38%, respectively, were considered responders regarding the primary criterion of efficacy, and 82%, 76% or 41% with respect to the secondary criterion. Nausea and vomiting were the most frequently reported adverse effects and were most often seen with (+)-tramadol. Taking into account both efficacy and adverse events, the racemate seems to be superior to either enantiomer alone.[89,90]

Lehmann performed multiple identical studies using different opioids in intravenous PCA and calculated equipotent dose ratios from hourly opioid consumption and retrospective pain score [65] The equipotent dose ratio of tramadol compared with morphine was between 6.3 : 1 and 10.2 : 1.[65]

In a pooled analysis of 18 single-dose studies on oral tramadol, nine in dental extraction pain (1594 patients) and nine in postsurgical pain (1859 patients), tramadol 50mg showed similar analgesic efficacy to codeine 60mg, and tramadol 100mg was the optimal single dose for acute pain.[92] Because tramadol has a higher oral bioavailability than morphine, an equipotent dose ratio of 4 : 1 for oral tramadol compared with oral morphine should be expected.

2.3 Effects on Respiration

Tramadol, as a μ opioid agonist, influences respiration but is unlikely to produce clinically relevant respiratory depression at the recommended dosage. In healthy volunteers, tramadol reduces total ventilatory CO_2 sensitivity by acting at μ opioid receptors in the brainstem,[93] but does not depress the hypoxic ventilatory response.[94] Furthermore, tramadol exhibited a minimum effect on respiration and breathing pattern when given as a 150mg bolus plus a subsequent 3-hour steady infusion of 250mg.[95]

In spontaneously breathing anaesthetised patients, tramadol 0.6 mg/kg had no effects on end-tidal CO_2 concentration, minute volume and respiratory rate, whereas equianalgesic doses of oxycodone or pethidine produced respiratory depression.[96,97] In children under halothane anaesthesia, intravenous tramadol 1 or 2 mg/kg caused significantly less respiratory depression than intravenous pethidine 1 mg/kg.[98]

2.4 Haemodynamic Effects

Tramadol has no clinically relevant haemodynamic effects. In healthy volunteers, blood pressure and heart rate were only very slightly and transiently elevated following intravenous tramadol 100mg.[99] A bolus of 150mg plus a subsequent 3-hour steady infusion of 250mg did not have any clinically significant effects on haemodynamics in volunteers, but an increase in plasma epinephrine levels was noted.[95] During artificial ventilation with oxygen and nitrous oxide before the start of surgery, intravenous tramadol 0.75 and 1.5 mg/kg caused a minor increase in systemic and pulmonary blood pressure.[100] Intravenous tramadol 0.6 mg/kg and oxycodone 0.04 mg/kg had no significant effect on heart rate in spontaneously breathing patients during halothane anaesthesia.[101]

No major effects on heart rate, mean pulmonary artery pressure, pulmonary capillary wedge pressure, stroke volume index and total peripheral resistance were observed in 57 circulatory risk patients prior to major vascular surgery following equipotent doses of morphine, fentanyl, alfentanil, tramadol and nalbuphine.[102] Furthermore, tramadol 50mg administered intravenously produced no significant change in heart rate and blood pressure in patients

with myocardial infarction or unstable angina pectoris [103]

2.5 Gastrointestinal Effects

Tramadol, in contrast to other μ receptor agonists, has only a minor delaying effect on gastrointestinal transit. In healthy volunteers, tramadol 1 mg/kg did not delay gastric emptying.[104] In another study, tramadol 1.25 mg/kg had a measurable but smaller inhibitory effect on gastric emptying compared with morphine and codeine.[105] In a double-blind crossover study of ten healthy volunteers, tramadol 50mg and placebo solutions were given four times daily for 10 days.[106] In this longer-term study, tramadol had a minor delaying effect on colonic transit but no effect on upper gastrointestinal transit or gut smooth muscle tone.

In patients with pancreatitis, orocecal transit time was unchanged after 5 days of tramadol, but increased with morphine.[107] Gastrointestinal motility was also evaluated after abdominal hysterectomies in 50 patients who were randomised to receive double-blinded postoperative 48-hour infusions of morphine or tramadol.[108] Orocecal and colonic transit times increased after operation with both morphine and tramadol, but gastric emptying was prolonged only with morphine. Whereas pentazocine causes spasm of the bile duct sphincter, tramadol, buprenorphine and saline showed no such effect.[109]

2.6 Effects on Immune System

In rats, tramadol has an immunological profile different from that of morphine, which is known to suppress both natural killer cell activity and T lymphocyte proliferation at subanalgesic doses.[110] Tramadol significantly depressed T lymphocyte function at analgesic doses, but did not modify the activity of natural killer cells, which mediate cytotoxicity against tumour cells and are important in immune defence against viral infection.[110]

Another study demonstrated immunostimulatory properties of tramadol.[111] In contrast to morphine, tramadol increased natural killer cell activity in normal non-operated rats and was able to prevent surgery-induced suppression of natural killer cell activity.[111] Furthermore, tramadol given before and after surgery blocked the enhancement of lung metastasis induced by surgery in rats.[111]

After surgery in cancer patients, analgesic doses of tramadol, in contrast to morphine, returned the surgery-induced depression of T lymphocyte proliferation to basal levels.[112] In addition, tramadol enhanced the activity of natural killer cells.[112]

3. Therapeutic Efficacy in Acute Pain

Extensive studies reviewed previously[22,65] have demonstrated the analgesic efficacy and tolerability of orally, intramuscularly or intravenously administered tramadol in acute pain. Although tramadol has been used in post-traumatic, obstetric, and renal or biliary colic pain, most studies have investigated postoperative pain (table VI). In a meta-analysis that included, for methodical reasons, only three of 36 controlled trials on postoperative pain, an odds ratio of 0.4 (95% CI −0.60, 0.86) demonstrated the analgesic efficacy of tramadol compared with placebo and morphine.[113]

3.1 Postoperative Pain

3.1.1 Oral Administration

A meta-analysis of published and unpublished data has demonstrated clear analgesic efficacy of single-dose oral tramadol.[142] In postsurgical pain, oral tramadol 50, 100 and 150mg had number needed to treat (NNT) of 7.1, 4.8 and 2.4, respectively, compared with aspirin 650mg plus codeine 60mg (3.6) and paracetamol (acetaminophen) 650mg plus propoxyphene 100mg (4.0).[142] This means that one in every 2.4–7.1 patients would experience at least 50% pain relief with tramadol, but would not have done so with placebo.

Two of these single-dose studies have been published in detail, but present contradicting results.[118,119] Oral tramadol 75 or 150mg was significantly more effective than placebo and a combination of paracetamol 650mg and propoxyphene 100mg in 161 patients following caesarean section.[119] Stubhaug et al.,[118] however, found no difference in analgesic efficacy between tramadol 50 or 100mg and placebo on the first day after total hip replacement in 144 patients, but significantly more emetic episodes after tramadol. The good test sensitivity of the latter study was confirmed by the active

control (paracetamol 1000mg plus codeine 60mg) being superior to tramadol and placebo. Explanations for the discrepancy between these two studies are that baseline pain intensity was obviously higher in the study of Stubhaug et al.[118] and that pain following hip surgery is somatic whereas pain following caesarean section also includes visceral pain. Thus, a single oral dose of tramadol does not seem to be adequate in severe pain following orthopaedic surgery. Multiple doses of oral tramadol 50–200mg, however, provided effective analgesia on the day after prolapsed intervertebral disc repair in 80 patients with severe pain, with no difference in pain relief or adverse events to oral pentazocine 50–200mg.[116]

The analgesic efficacy of oral single-dose tramadol can be increased by combination with a non-opioid analgesic. A meta-analysis of seven randomised, double-blind, placebo-controlled trials compared the combination of tramadol 75 or 112.5mg plus paracetamol 650 or 975mg with its components in postoperative pain.[143] Combination analgesics (tramadol plus paracetamol) had significantly better NNTs than the components alone and a similar rate of adverse events.

Oral tramadol has also been demonstrated to be effective following surgery in children. Oral tramadol 1.5 mg/kg provided postoperative analgesia superior to that of placebo in 60 children undergoing extraction of six or more teeth.[144] In another study, 81 postsurgical patients 7–16 years of age received oral tramadol 1 or 2 mg/kg for postoperative analgesia when they were ready to convert from morphine PCA to oral analgesics.[145] The 2 mg/kg group required approximately half as much rescue analgesia as did the 1 mg/kg group. Adverse events were similar between the two treatment groups. In a single-blind study of children aged 11 years and older, oral tramadol delivered the same analgesic efficacy as oral diclofenac for post-tonsillectomy pain relief.[146]

Oral tramadol is a suitable analgesic in patients undergoing day surgery, because the lack of respiratory depressant effect allows its use after discharge from hospital. In a double-blind, multicentre study, 111 patients were treated with oral tramadol 100–400 mg/day after discharge from groin surgery and 117 patients were treated with oral codeine/paracetamol 16/1000 mg/day.[114] Prior to discharge, the patients received pre-, intra- and postoperatively, either tramadol 100mg or fentanyl intravenously. Tramadol provided analgesic efficacy superior to that of fentanyl plus codeine/paracetamol. In a double-blind study of 91 gynaecological patients, oral tramadol 100mg administered pre- and postoperatively provided similar analgesic efficacy compared with oral naproxen 500mg administered pre- and postoperatively.[117] Well-being improved significantly in the tramadol group compared with the naproxen group. In another double-blind study, postoperative administration of tramadol 50–100mg every 4–6 hours provided efficacy similar to that of a combination of paracetamol/codeine 500/30mg or paracetamol/dextropropoxyphene 325/32.5mg in 68 patients who underwent laparoscopic surgery.[115]

3.1.2 Rectal Administration

The use of rectal tramadol administration was investigated in only one study of 40 patients.[147] There was no difference in pain scores at rest and during movement between tramadol suppositories 100mg or paracetamol/codeine suppositories 1000/20mg every 6 hours, but the incidence of nausea and vomiting was significantly higher in the tramadol-treated group (84% vs 31%).

3.1.3 Intramuscular Administration

Early studies in 1981 demonstrated the analgesic effects of single-dose intramuscular tramadol 50–100mg.[120,123] Several recent studies have confirmed that repeated intramuscular administration of tramadol can provide effective and well tolerated postoperative analgesia comparable to that obtained with morphine, pentazocine and ketorolac.[112,121,124,126,127] In contrast, multiple intramuscular injections of codeine 60mg provided better analgesia than tramadol 50 or 75mg after craniotomy.[125] In addition, tramadol 75mg was associated with increased sedation, nausea and vomiting.[125] A potential explanation for this discrepancy could be that pain after craniotomy is less responsive to serotonin and norepinephrine reuptake inhibition, which is part of the mechanism of action of tramadol.

The intramuscular administration of tramadol 150mg also improved lung function in 20 patients receiving dipyrone 2g every 6 hours intravenously following laparoscopic cholecystectomy[122] and in-

Table VI. Controlled trials of tramadol in postoperative pain

Study	Type of surgery	Study design	n	Analgesic drug	Dosage (mg/day)	Analgesic efficacy
Oral administration						
Bamigbade et al.[114]	Groin	db	228	Tramadol	100–400	T > C/P
				Codeine/paracetamol	16–64/1000–4000	
Crighton et al.[115]	Laparoscopy	db	68	Tramadol	50–400	T = C/P = DP/P
				Codeine/paracetamol	30–240/500–4000	
				Dextropropoxyphene/paracetamol	32.5–260/325–2600	
Kupers et al.[116]	Orthopaedic	db	160	Tramadol	50	T = PE
				Pentazocine	50	
Peters et al.[117]	Gynaecological	db	91	Tramadol	150–200	T > N
				Naproxen	750–1000	
Stubhaug et al.[118]	Orthopaedic	db, sd	144	Tramadol	50 or 100	C/P > T = PL
				Codeine/paracetamol	60/1000	
				Placebo		
Sunshine et al.[119]	Section	db, sd	161	Tramadol	75 or 150	T > PR/P > PL
				Propoxyphene/paracetamol	100/650	
				Placebo		
Intramuscular administration						
Aton et al.[120]	General	db, sd	60	Tramadol	50	T < B
				Buprenorphine	0.3	
Collatti et al.[121]	Nasal	nb	77	Tramadol	100–400	T = K
				Ketorolac	30–90	
de La Pena et al.[122]	Laparoscopic cholecystectomy	db, sd	20	Tramadol	50	T > P
				Placebo		
Fassoi[123]	General	db, sd	75	Tramadol	100	T = PE
				Pentazocine	30	
Grilli et al.[124]	Abdominal	nb	70	Tramadol	100–600	T = M
				Morphine	10–60	
Jeffrey et al.[125]	Craniotomy	db	75	Tramadol	50	T < C
				Tramadol	75	
				Codeine	60	
Lanzetta et al.[126]	Orthopaedic	nb	48	Tramadol	100–400	T = K
				Ketorolac	30–90	
Magrini et al.[127]	Various	nb	50	Tramadol	300	T > PE
				Pentazocine	90	

Continued next page

Table VI. Contd

Study	Type of surgery	Study design	n	Analgesic drug	Dosage (mg/day)	Analgesic efficacy
Saccardote et al.[112]	Abdominal	db, sd	30	Tramadol	100	T = M
				Morphine	10	
Intravenous administration						
Bloch et al.[124]	Thoracotomy	db	89	Tramadol (+ morphine PCA)	150 + 350/24h	T = ME > PL
				Morphine epidural (+ morphine PCA)	2 + 0.2/h	
				Placebo (+ morphine PCA)		
Dejonckheere et al.[125]	Thyroidectomy	db	80	Tramadol	1.5 mg/kg	T > PP
				Propacetamol	2000	
Driessen et al.[126]	Vaginal hysterectomy	nb, sd	27	Tramadol	50	T < PE < B
				Buprenorphine	0.3	
				Pentazocine	30	
Houmes et al.[127]	Gynaecological	db	150	Tramadol	50–150	T = M
				Morphine	5–15	
Marji et al.[128]	Cardiac	nb	56	Tramadol	100–600	T = A
				Alfentanil	12.5 µg/kg/h	
Olla et al.[129]	Abdominal hysterectomy	db	76	Tramadol	400	T > K
				Ketorolac	120	
Putland and McCluskey[130]	Laparoscopy	db, sd	60	Tramadol	1.5 mg/kg	T > K
				Ketorolac	10	
Ranucci et al.[131]	Cardiac	db	60	Tramadol	200	T = K > PP
				Ketorolac	60	
				Propacetamol	2000	
Sellin et al.[132]	Cardiac	db	100	Tramadol	360–600	T = M
				Morphine	24 + 2 pm	
Stankov et al.[133]	Urological	db, sd	100	Tramadol	100	T < D
				Dipyrone	2500	
Strebel et al.[134]	Vaginal hysterectomy	db	60	Tramadol/dipyrone	400/5000	T/D = T/I
				Tramadol/ibuprofen	400/585	
Torres et al.[135]	Abdominal hysterectomy	db	151	Tramadol	100–400	T = D
				Dipyrone	1000–8000	
Tryba and Zenz[145]	Orthopaedic	db	60	Tramadol	50–100	T = M = CL
				Morphine	5–10	
				Clonidine	0.15–0.3	
Vickers and Paravicini[144]	Abdominal	db	523	Tramadol	100–650	T = M
				Morphine	5–60	

A = alfentanil; B = buprenorphine; C = codeine; CL = clonidine; D = dipyrone; db = double-blind; DP = dextropropoxyphene; I = ibuprofen; K = ketorolac; M = morphine; ME = morphine epidural; N = naproxen; nb = nonblind; P = paracetamol; PCA = patient-controlled analgesia; PE = pentazocine; PL = placebo; PP = propacetamol; PR = propoxyphene; prn = as needed; sd = single dose; T = tramadol; > indicates superior to; = indicates equivalent to; < indicates inferior to.

tramuscular administration of tramadol 100mg could improve postoperative immune suppression.[112]

3.1.4 Intravenous Administration

In an early study, a single intravenous bolus injection of tramadol 50mg was inferior to buprenorphine 0.3mg for pain relief after vaginal hysterectomy.[130] The authors suggested that tramadol doses >50mg might be necessary in many patients. In two other studies, two or three intravenous bolus doses of tramadol 50mg provided acceptable analgesia, which was similar to the effects of morphine 5mg.[131,140] In a double-blind randomised study involving 523 patients, the analgesic efficacy of tramadol (up to 650 mg/day) was compared with that of morphine (up to 60 mg/day) given as repeated intravenous boluses as required to control pain following abdominal surgery.[141] Responder rates reached 72.6% with tramadol and 81.2% with morphine, and the treatments were statistically equivalent.

In two double-blind comparative studies, continuous intravenous infusion of tramadol 12 mg/h showed a trend towards better pain relief than with intermittent intravenous bolus doses of tramadol 50mg following abdominal surgery.[148,149] Although total consumption of tramadol was more than 30% higher with the continuous infusion, the rate of adverse events was not increased.[148,149] Two other studies demonstrated that continuous infusion of tramadol, titrated to the patient's requirements, provides adequate analgesia after cardiac surgery, comparable with the effects of alfentanil or morphine infusion.[132-136] In two recent studies, the addition of a tramadol infusion to morphine PCA improved analgesia and reduced morphine requirements after abdominal or thoracic surgery.[128,150] No differences were found with regard to nausea or sedation after abdominal surgery.[150] For the management of post-thoracotomy pain, 90 patients received, in addition to morphine PCA, either intravenous tramadol (150mg bolus followed by infusion, total 450 mg/day), epidural morphine (2mg, then 0.2 mg/h) or nothing.[128] Pain scores at rest and on coughing were lower in the tramadol and epidural morphine groups than in the placebo (only PCA morphine) group. The authors concluded that an intraoperative bolus of tramadol followed by an infusion was as effective as epidural morphine and avoided the necessity of placing a thoracic epidural catheter.

The continuous intravenous infusion of tramadol 0.25 mg/kg/h was also shown to be a simple and well tolerated procedure following urological surgery in children.[151]

Several studies have compared the efficacy of intravenous tramadol with that of non-opioid analgesics. A single dose of tramadol 1.5 mg/kg provides a better quality of analgesia than that with propacetamol 2g during the first 6 hours after thyroidectomy.[129] In an observer-blind randomised study, single intravenous doses of tramadol 100mg produced less pain relief after abdominal or urological surgery than intravenous dipyrone, which possesses spasmolytic effects.[137] Another study used an intravenous loading dose immediately after abdominal hysterectomy followed by intravenous maintenance infusion and on-demand boluses up to a maximum of either dipyrone 8 g/day or tramadol 500 mg/day.[139] Both drugs showed similar efficacy for early pain, but tramadol caused nausea and vomiting more frequently. An intravenous bolus of tramadol 1.5 mg/kg was more effective than ketorolac 10 mg/kg following laparoscopic sterilisation in 60 patients.[134] No difference in either the incidence or severity of nausea and vomiting was observed between the two groups. In 76 women undergoing abdominal hysterectomies, the intravenous injection of tramadol 100mg every 6 hours provided more effective pain relief than that with ketorolac 30mg, but was associated with a high incidence of postoperative vomiting.[133] A randomised trial was aimed at investigating the effectiveness of intravenous ketorolac 60mg, propacetamol 2g and tramadol 200mg for the management of postoperative pain in early extubated cardiac surgical patients.[135] There was a significantly higher rate of patients with severe pain in the propacetamol group. Patients treated with tramadol had a higher arterial partial pressure of CO_2, which was not clinically relevant and can be explained by the relatively high dose of 200mg.

The infusion of a fixed combination of tramadol and non-opioids, which is very popular in Germany, has been investigated in only one controlled study.[138] This study compared a tramadol/dipyrone

infusion (400mg/5g in 500mL) with a tramadol infusion (400mg in 500mL) in combination with rectal ibuprofen 585mg.[138] In 60 patients recovering from vaginal hysterectomy, satisfactory pain reduction occurred rather late, although 60% of the 500mL was administered within 60 minutes. The authors concluded that neither regimen could be recommended for fast onset of adequate analgesia. Another fixed combination, tramadol 600mg and ketorolac 180mg diluted to a volume of 96mL and intravenously infused at a constant rate of 2 mL/h, was investigated in 585 patients following major abdominal surgery.[152] Supplementary tramadol 100–300 mg/day was injected on request. The average pain intensity (verbal numeric scale 0–10) was below 3 at rest and below 4 on movement, which was interpreted as good quality of pain relief by the authors of this uncontrolled trial.[152]

Intravenous tramadol reduces not only postoperative pain but also postoperative shivering. Several double-blind controlled studies demonstrate that intravenous tramadol 0.7–2.5 mg/kg can prevent the severity and prevalence of postanaesthetic shivering in a dose-dependent manner.[132,153-156] Tramadol 1 mg/kg was superior to pethidine 0.5 mg/kg.[153] Furthermore, intravenous tramadol reduced shivering during regional anaesthesia of obstetric patients in two controlled double-blind studies.[157,158]

In an early double-blind study on the intraoperative use of tramadol, 65% of the patients receiving tramadol were aware of intraoperative music whereas patients in the placebo group were amnesiac.[159] Therefore, tramadol was not recommended as the sole agent for intraoperative analgesia. Several recent studies on the intraoperative use of tramadol in combination with volatile or intravenous anaesthetics have shown no clinically relevant lightening of anaesthetic depth.[160-164] Preoperative administration of morphine 10mg was more effective than tramadol 100mg as an intraoperative analgesic, but there was no difference in the postoperative pain treatment.[160] Other studies demonstrated that intravenous tramadol administered at wound closure provided postoperative analgesia superior to that with placebo[161,162] and similar to that with intravenous[163] or epidural[164] morphine.

Several studies have investigated the intravenous injection of tramadol 0.5–3 mg/kg at induction of anaesthesia in children.[165-169] In adenoidectomy and/or tonsillectomy, pre-emptive tramadol provided posterior analgesia superior to that with placebo[165,167,169] or propacetamol.[166] Tramadol 3 mg/kg was inferior to pethidine 1.5 mg/kg and nalbuphine 0.3 mg/kg in tonsillo-adenoidectomy,[169] and tramadol 1 mg/kg was inferior to fentanyl 2 μg/kg/h in paediatric neurosurgery.[168]

Intravenous tramadol is also effective in preventing the pain of propofol injection.[170,171] The combination of tramadol with lidocaine for intravenous regional anaesthesia had only a limited benefit and cannot be recommended.[172-175]

3.1.5 Patient-Controlled Analgesia

PCA allows the patients to self-administer small bolus doses of a potent analgesic in a running intravenous infusion.[176] Whenever the patients feel that pain relief is necessary, they can activate an electronically controlled infusion pump that dispenses a preprogrammed amount of analgesic. A controlled study of 20 patients undergoing gynaecological operations compared tramadol PCA (loading dose 3 mg/kg, demand dose 30mg, lock-out time 5 minutes, concurrent infusion 5 mg/h) and tramadol continuous infusion (loading dose 3 mg/kg, continuous infusion 0.35 mg/kg/h).[177] PCA ensured adjustment of the medication to the individual demand, whereas continuous infusion provided better analgesia after sleeping periods.[177]

Table VII summarises the controlled trials of PCA with tramadol, demonstrating its feasibility in postoperative pain. Most studies compared tramadol with other opioids, used a tramadol demand dose of 10–50mg and investigated pain following abdominal or orthopaedic surgery. In the only placebo-controlled study of intravenous PCA, tramadol and morphine proved to be efficacious.[178] Of 180 patients recovering from abdominal surgery, 68%, 75% and 18% of patients treated with tramadol, morphine and placebo, respectively, were assessed as responders. In five PCA studies comparing intravenous tramadol and morphine, the equipotent dose ratio was between 9 : 1 and 19 : 1.[160,179-182] Another study compared tramadol and morphine via subcutaneous PCA following major orthopaedic

surgery in 40 patients.[25] Both drugs provided effective analgesia; the mean consumption in the first 24 hours was 792mg of tramadol and 42mg of morphine. Whereas tramadol is associated more frequently with nausea and vomiting, morphine has a higher risk of respiratory depression.[25,179-182]

Double-blind PCA studies comparing tramadol with other opioids reported an equipotent dose ratio of 5 : 1 for tramadol : nalbuphine, 979 : 1 for tramadol : fentanyl, 1.1–1.2 : 1 for tramadol : pethidine and 8 : 1 for tramadol : oxycodone.[63,183,184,190,191]

Several studies have investigated methods to reduce the rate of nausea during tramadol PCA. Administering the loading dose of tramadol during surgery decreases the risk of nausea/vomiting and improves the quality of tramadol PCA in the relief of postoperative pain.[192] A tramadol and droperidol combination is superior to tramadol alone for postoperative PCA.[193] It provides a similar quality of analgesia with less nausea and vomiting and without an increase in sedation. When ondansetron was administered for antiemetic prophylaxis, the tramadol requirement during PCA was increased.[88]

The analgesic effect of tramadol in postoperative PCA can further be improved by a combination with non-opioid analgesics. The combination of tramadol and dipyrone was superior to piritramide.[185] A further study included 101 post-hysterectomy patients who, at the time of analgesia request, received tramadol 100mg or dipyrone 1.2g alone, or combined in 1 : 1, 1 : 0.3 or 1 : 3 ratio.[187] After 15 minutes, they received the same treatment by PCA. When drugs were combined in a 1 : 1 ratio, synergy was present for the analgesic effects, but also for adverse events; all other treatments were additive. Tramadol PCA in combination with intravenous propacetamol 2g four times daily provided analgesia superior to that of tramadol monotherapy.[186] Another randomised double-blind study compared PCA with tramadol and PCA with a mixture of tramadol plus lysine acetylsalicylate (a soluble aspirin) in 50 adult patients who had undergone major orthopaedic surgery.[188] Total tramadol consumption was significantly less and patients were more alert in the aspirin group. One study of PCA has compared tramadol with non-opioid analgesics.[189] According to patient global assessment, 72% of patients in the tramadol group assessed analgesia as excellent or very good, compared with 58% with ketorolac, 50% with clonixin and 55% with dipyrone.

3.1.6 Regional Administration

Only a few studies are available on epidural tramadol,[194-197] a mode of administration for which tramadol is not registered. Two placebo-controlled studies demonstrated that epidural tramadol 50 and 100mg provided adequate postoperative analgesia after caesarean delivery.[194,198] After abdominal surgery, epidural tramadol 100mg produced better pain relief than tramadol 50mg or 10mL of 0.25% buprenorphine[196] and was not different from morphine 4mg.[197] However, ineffective analgesia from epidural tramadol 50 and 100mg was reported in patients undergoing total knee replacement.[195]

Tramadol 1–2 mg/kg has also administered caudally in children for postoperative analgesia.[199-203] Caudal tramadol 2 mg/kg provided reliable postoperative analgesia similar to that with caudal morphine 0.03 mg/kg in children who were undergoing herniorrhaphy.[199] Although in two studies tramadol was less effective than caudal bupivacaine 0.2–0.25%,[200,203] one study reported comparable effects.[201] In another study, lower pain scores were seen with caudal bupivacaine 0.25% in the immediate postoperative period, whereas caudal tramadol caused a significantly lower pain score in the late postoperative period.[202] The combination of both drugs improved the analgesic action of bupivacaine in only one[200] of three studies.[200,201,203]

Prompted by the success of intra-articular morphine, tramadol 10mg was used intra-articularly after arthroscopic knee surgery in a double-blind study and provided effective pain relief, although morphine 1mg was more effective.[204] Another study demonstrated that the admixture of tramadol 100mg with mepivacaine 1% for brachial plexus block provided a pronounced prolongation of blockade without adverse effects.[205]

3.2 Other Acute Pain Syndromes

3.2.1 Trauma

Several reports describe positive experiences with tramadol for orthopaedic trauma,[206] winter sports injuries[207] and use in the prehospital situation by ambulance paramedics.[208] A double-blind study found no difference in the efficacy of tramadol

100–200mg and morphine 5–20mg administered intravenously for the management of pain in 105 trauma patients in the prehospital situation [209] In a controlled trial, intravenous tramadol 1 mg/kg, propacetamol 20 mg/kg and diclofenac 1 mg/kg were equally efficacious for emergency analgesic treatment of 131 patients [210] In the piritramide group (0.25 mg/kg), significantly more adverse effects were noted.

3.2.2 Abdominal Pain

Parenteral tramadol in emergency department patients with abdominal pain in the right lower quadrant resulted in pain reduction without concurrent normalisation of abdominal examination findings indicative of acute appendicitis.[211] Several controlled studies have demonstrated the efficacy of tramadol in colic pain [212-216] In renal and biliary colic pain, intravenous dipyrone 2.5g was superior to tramadol 100mg and butylscopolamine 20mg [214,215] In another study, tramadol 100mg was as effective as dipyrone 2.5g for ureteric colic.[216] In acute renal colic pain, intravenous pethidine 50mg was superior to tramadol 50mg[212] and intramuscular ketorolac 30mg was as effective as subcutaneous tramadol 1 mg/kg.[213]

3.2.3 Labour

Elbourne and Wiseman[217] searched the Cochrane Library in 1997 and assessed 16 randomised trials comparing the effects of different currently used opioids administered intramuscularly in labour for women who requested systemic analgesia. They found no evidence of a difference between pethidine and tramadol in terms of pain relief, interval to delivery, or instrumental or operative delivery. There appeared to be more adverse effects such as nausea, vomiting and drowsiness with pethidine.

Intramuscular tramadol 100mg, but not 50mg, provided pain relief equivalent to that with pethidine 75mg.[218] With pethidine, adverse effects were more frequent and respiratory function of the neonates was significantly lower. Another study found no differences in analgesic efficacy, incidence of adverse effects, umbilical cord blood gases or Apgar scores between tramadol 100mg and pethidine 50mg [219] Other authors confirmed that tramadol resulted in analgesia equivalent to that with pethidine without respiratory depression in mothers and neonates.[29,220-223] Intravenous tramadol 50–100mg in the first stages of labour produced respiratory depression in only 7% of neonates, compared with 31% in the pethidine group.[224] This study is unusual with regard to the high rate of respiratory depression in both groups Tramadol suppositories have also been recommended for obstetrical analgesia [225]

3.3 Place of Tramadol in Acute Pain

The treatment of acute pain is not only important for the well-being of patients, it also reduces the risk of complications such as pneumonia, cardiac infarction or thromboembolism and may improve the outcome.[226] Besides regional analgesia, which is invasive and only suitable for selected patients, the administration of opioids is the most common approach to treat postoperative pain

Tramadol provides adequate analgesia in acute pain, being superior to placebo and comparable with various opioid and non-opioid analgesics in the majority of studies (table VI and table VII). Therefore, tramadol can be recommended as a basic analgesic for the treatment of moderate-to-severe acute pain.

Intravenous infusion or intravenous PCA are indicated in severe pain following surgery. Although intramuscular tramadol is effective, the injection is painful and systemic absorption might be delayed in the early postoperative period; therefore, oral or intravenous administration may be preferred. Drops or capsules are a good choice when enteral administration is possible after surgery, particularly in day case surgery. Further indications for systemic tramadol include postanaesthetic shivering, post-traumatic pain, labour pain and colic pain. In addition, oral and intravenous tramadol appears to be an effective and well tolerated analgesic agent in children with postoperative pain. The good analgesic effects achieved by caudal administration can be explained by extensive systemic absorption,[37] and no advantages over systemic administration can be expected

In contrast to the majority of studies (table VI and table VII), tramadol did not equal the analgesic efficacy of other drugs in all circumstances A single dose of tramadol was not different from placebo in a

Table VII. Controlled trials of patient-controlled analgesia with tramadol in postoperative pain

Study	Surgery (duration of PCA [h])	Drug	n	Loading dose (mg)	Infusion rate (mg/h)	Demand dose (mg) [lock-out (min)]	Mean cumulative dose (mg)	Analgesic efficacy (relative potency)
Alon et al.[156]	Abdominal hysterectomy (5)	Tramadol	20	50	25	25 (30)	373	T = N (1 : 5)
		Nalbuphine	20	10	5	5 (30)	73	
Hackl et al.[6]	Cholecystectomy (6)	Tramadol	7	0	12	20	412	T = F (1 : 979)
		Fentanyl	10	0	0.054	0.009	0.53	
Lehmann et al.[154]	Various (18)	Tramadol	40	0	1.15	9.6 (1)	203	T = PE (1 : 1.2)
		Pethidine	40	0	1.15	9.6 (1)	175	
Likar et al.[155]	Orthopaedic (24)	Tramadol/dipyrone	18	164/1030	0	10/50 (6)	257/1335	T/D > PI
		Tramadol/dipyrone	19	72/462	0	5/25 (6)	256/1275	
		Piritramide	21	7.5	0	1.5 (6)	44	
		Piritramide	20	4.5	0	0.75 (6)	37	
Migliorini et al.[154]	Orthopaedic (24)	Tramadol	35	0	10	50 (15)	489	T < T/PP
		Tramadol + propacetamol 2g qid	35	0	10	50 (15)	426	
Montes et al.[157]	Abdominal hysterectomy (24)	Tramadol	21	100	0	20 (15)	NR	T/D (1 : 1) > T = D = T/D (1 : 0.3) = T/D (0.3 : 1)
		Dipyrone	21	1200	0	240 (15)	NR	
		Tramadol/dipyrone (1 : 1)	20	50/600	0	10/120 (15)	NR	
		Tramadol/dipyrone (1 : 0.3)	19	75/300	0	15/60 (15)	NR	
		Tramadol/dipyrone (0.3 : 1)	20	25/900	0	5/180 (15)	NR	
Naguib et al.[152]	Laparoscopy (24)	Tramadol	50	100	0	16 (5)	248	T = M (1 : 13)
		Morphine	50	10	0	1.6 (5)	20	
Ng et al.[153]	Abdominal (48)	Tramadol	19	0	0	10 (5)	9.6/h	T = M (1 : 9)
		Morphine	19	0	0	1 (5)	1.1/h	
Pang et al.[155]	Orthopaedic (48)	Tramadol	40	285	0	30 (10)	868	T = M (1 : 19)
		Morphine	40	13	0	1 (10)	46	
Pang et al.[158]	Orthopaedic (48)	Tramadol	25	2.5 mg/kg	0		923 (T)	T < T/AS
		Tramadol/aspirin	25	1.25/12.5 mg/kg	0		614 (T)	
Rodriguez et al.[151]	Abdominal hysterectomy (24)	Tramadol	40	30	15	15 (NR)	NR	T = K = D > CL

Continued next page

Table VII. Contd

Study	Surgery (duration of PCA [h])	Drug	n	Loading dose (mg)	Infusion rate (mg/h)	Demand dose (mg) [lock-out (min)]	Mean cumulative dose (mg)	Analgesic efficacy (relative potency)
		Ketorolac	40	10	5	5 (NR)	NR	
		Clonixin	40	30	15	15 (NR)	NR	
		Dipyrone	40	650	330	330 (NR)	NR	
Silvasti et al.[161]	Breast (36)	Tramadol	25	51	0	450 µg/kg (5)	677	T = M (1 : 11)
		Morphine	18	6	0	45 µg/kg (5)	61	
Silvasti et al.[166]	Maxillofacial (24)	Tramadol	27	38	0	300 µg/kg (5)	200	T = O (1 : 6)
		Oxycodone	25	3	0	30 µg/kg (5)	25	
Stamer et al.[167]	Abdominal (48)	Tramadol	60	145	0	20 (5)	650	T = M > PL (1 : 12)
		Morphine	60	12	0	2 (5)	62	
		Placebo	60	17mL	0	1mL (5)	97mL	
Vickers et al.[191]	Abdominal (24)	Tramadol	20	0	0	20 (5–10)	624	T = PE (1 : 1.1)
		Pethidine	10	0	0	20 (5–10)	606	

AS = aspirin; CL = clonixin; D = dipyrone; F = fentanyl; K = ketorolac; M = morphine; N = nalbuphine; NR = not reported; O = oxycodone; PCA = patient-controlled analgesia; PE = pethidine; PI = piritramide; PL = placebo; PP = propacetamol; qid = four times daily; T = tramadol; > indicates superior to; = indicates equivalent to; < indicates inferior to.

study of severe pain following orthopaedic surgery,[118] and tramadol was less effective than codeine after craniotomy,[125] less effective than dipyrone after abdominal urological surgery,[137] less effective than pethidine or nalbuphine after tonsillo-adenoidectomy in children,[169] and less effective than fentanyl in paediatric neurosurgery.[168] The discrepancy in the results can mainly be attributed to different baseline pain intensity, different type of pain, different criteria of efficacy, and different doses and potencies of the active drug control. These results emphasise that the analgesic efficacy of tramadol should be monitored, as that of any other opioid, and that the dosage requires titration up to individual need by repeated oral administration, repeated injections, adaptation of a continuous infusion or intravenous PCA.

The analgesic efficacy of tramadol can be increased by combination with non-opioid analgesics such as paracetamol, dipyrone or ketorolac.[143,152,186-188] Following a suggestion of Krimmer et al.,[227] an infusion of a fixed combination of tramadol 300–400mg and dipyrone 2.5–5g in 500mL of saline over 12–30 hours is frequently used in Germany.[65] Despite the widespread application of this simple-to-use combination, which is usually given in general wards without close supervision, no controlled studies investigating the risk/benefit ratio of such combinations are available. If tramadol at dosages of 400–600 mg/day provides no adequate pain relief, administration of a stronger opioid, such as morphine, is necessary and useful.[150]

Nausea and vomiting are typical adverse effects with opioids. Although some studies found that tramadol is associated with an increased risk,[118,125,147,179,181] others reported no difference in the incidence of nausea and vomiting between tramadol and other opioids.[114,116,124,127,132,160] The rate of postoperative nausea and vomiting, however, depends only partly on the type of opioid; other major factors include dose, time and mode of opioid administration, pain intensity, type of surgery, type of anaesthesia and history of motion sickness. The rate of nausea and vomiting can be reduced by prophylactic administration of antiemetics, but unfortunately droperidol has been withdrawn and ondansetron reduces the analgesic efficacy of tramadol. There is lack of evidence whether trifluopromazine,

dimenhydrinate, metoclopramide or other antiemetics have a better risk/benefit ratio in combination with tramadol. One study showed that nausea and vomiting with tramadol occurred more frequently during the 15 minutes after the initial injection of the loading dose than during the PCA period, when boluses were infused over 2 minutes.[178] The authors concluded that a slower injection could avoid some nausea and vomiting. This hypothesis is in agreement with personal experiences of many doctors, but has not been investigated. Another approach to reduce the rate of postoperative nausea and vomiting is to inject the first tramadol bolus intraoperatively at wound closure.[162,163,192]

Tramadol demonstrates similar analgesia to that of several non-opioid analgesics (table VI). Although it is associated with a higher risk of typical opioid adverse effects, such as nausea, it may prove particularly beneficial in patients in whom non-opioid analgesics are not appropriate, including patients predisposed to peptic ulcers, with haemorrhagic disorders, hypertension and renal insufficiency.[22]

The most important advantage of tramadol over morphine and other opioids is its minimal effect on respiratory function.[25,97,131,141,179-182,191,228] Therefore, tramadol is a very good choice for children, in day-surgery, in normal wards without close supervision, in labour pain and in traumatic pain. In addition, tramadol improves lung function after laparoscopy[122] and thoracotomy;[128] in the latter study it was similar to epidural morphine. Patients with an increased risk of respiratory dysfunction, such as the elderly, smokers, those with pre-existing cardiopulmonary disease and those after surgery of the thorax or upper abdomen causing a decreased residual reserve, are expected to benefit particularly from this advantage. Further studies comparing equianalgesic doses of different opioids and carefully assessing adverse events are needed to confirm the influence of tramadol on postoperative convalescence in these situations.

Another advantage of tramadol is its low gastrointestinal inhibition.[108] Tramadol is, therefore, expected to improve gastrointestinal recovery from abdominal surgery and reduce the risk of postoperative paralysis and ileus compared with other opioids.

Recently, tramadol was shown to have positive effects on immune system function.[110,112,229] Therefore, tramadol might be a better choice than morphine, particularly in patients with compromised immunity or cancer. Further studies are required to confirm these preliminary results.

4. Chronic Pain

Chronic pain requires regular administration of analgesics. Only studies on the oral administration of tramadol over a period of at least 1 week can investigate its utility in the treatment of chronic pain. Therefore, single-dose studies and studies on parenteral administration have not been included in the following discussion. The controlled studies have been summarised in table VIII. In a meta-analysis, which, for methodical reasons, included only two of six controlled trials on cancer pain and three of ten controlled trials on chronic non-cancer pain, odds ratios of 0.49 (95% CI −0.36, 0.8) and 0.57 (95% CI 0.23, 0.9), respectively, demonstrated the analgesic efficacy of tramadol compared with placebo and morphine.[113]

4.1 Cancer Pain

Three noncomparative studies have demonstrated the efficacy of oral tramadol in cancer pain.[232,250,251] Of 30 patients with different malignant diseases, 86% had excellent or adequate pain relief after the administration of tramadol up to 200 mg/day.[250] In another study, 51 cancer patients were treated with oral or intramuscular tramadol 300 mg/day for periods of 2 weeks to 14 months.[251] Eighty-three percent of patients with bone pain and 62% of patients with visceral pain, but only 33% of patients with neuropathic pain, reported good analgesia. In another open study, tramadol was used in 294 cancer patients in whom non-opioids alone failed to provide sufficient analgesia.[232] As recommended by the WHO, tramadol was combined with non-opioid analgesics and co-analgesics where appropriate. Patients were treated with oral tramadol at 4-hour intervals at a dosage of between 250 and 600 mg/day for an overall period of 8227 days (mean 28 days). If pain could not be controlled with the maximum daily dosage of 600mg, a strong opioid was started (70% of patients). Tramadol was stopped

because of adverse events in only 4% of patients. On 78% of the treatment days, patients had no or only mild pain.

The effectiveness and tolerability of tramadol in the treatment of cancer pain has been confirmed in several studies comparing tramadol with morphine or buprenorphine (table VIII). A nonrandomised study compared 810 patients receiving high-dosage tramadol 300–600 mg/day for a total of 23 497 days with 848 patients receiving low-dosage morphine 10–60 mg/day for a total of 24 695 days.[252] The analgesic efficacy was good in 74% and 78% of patients receiving tramadol and morphine, respectively. Constipation, neuropsychiatric symptoms and pruritus were observed more frequently with morphine. This lower rate of typical opioid adverse effects can be explained by the multiple modes of action of tramadol. The recommended maximum dose of tramadol is 400 mg/day. Tramadol, however, is a pure agonist (with a low affinity) at μ opioid receptors and no ceiling effect has been determined. The above data demonstrate that tramadol dosages up to 600 mg/day are effective and well tolerated in the treatment of cancer pain. Higher dosages have not been investigated, although a further enhancement of the analgesic effects would be expected. They cannot be recommended because of a potentially increasing risk of specific and nonspecific adverse effects, such as seizures.

Osipova et al [233] compared 98 patients receiving tramadol (mean dosage 368 mg/day [stable dose throughout the study]) and 26 patients receiving SR morphine (mean dosage increased from 69 mg/day to 96 mg/day during the study) for relief of severe cancer pain. Tramadol was effective and well tolerated during a study period of 1–3 months in all patients with moderate pain and in 89% of the patients with severe pain. Morphine produced excellent to good analgesic efficacy in all patients, but was associated with more intense adverse effects. Similar results were observed by Tawfik et al.[234] investigating 32 patients being treated with tramadol (mean dosage 217 mg/day) and 32 patients treated with SR morphine (mean dosage 50 mg/day) for up to 8 weeks. Adequate pain relief was obtained with tramadol in 58–88% and with morphine in 67–100% of the patients. Insufficient analgesia was more frequent in the tramadol group, but tramadol caused fewer adverse effects. In a double-blind, randomised, crossover trial (2 × 4 days), 20 patients were treated with oral solutions of tramadol (mean dosage 375 mg/day) and morphine (mean dosage 101 mg/day).[235] Tramadol had the same efficacy but produced less nausea and constipation than morphine. Examination of doses used revealed a tendency to greater tolerance development with morphine than with tramadol.[233,234]

To compare the analgesic effect and tolerability of tramadol 300 mg/day and buprenorphine 0.6 mg/day, 60 cancer patients were treated orally in a controlled crossover trial (2 × 1 week).[230] Buprenorphine and tramadol had a similar analgesic effect; the incidence of adverse effects such as constipation and respiratory depression was lower with tramadol. Only one patient discontinued tramadol compared with 18 using buprenorphine. The final assessment was significantly in favour of tramadol as regards efficacy and patient acceptability.

4.1.1 Sustained-Release

SR formulations are given at intervals of 8–12 hours and are, therefore, of special interest for the treatment of chronic pain. An open noncomparative study proved the analgesic efficacy of SR tramadol with administration every 12 hours to patients with moderate-to-severe cancer pain.[253] Of 146 patients, 62% completed the 6-week trial period; 20% discontinued because of adverse events, 9% because of inadequate pain relief, 3% because of both reasons and 6% because of other reasons. The number of patients with good and complete pain relief increased from 43% after week 1 to 71% after week 6 with daily dosages of tramadol up to 650mg. Most patients (86%) experienced adverse events during the study period. Nausea and vomiting were most frequently reported, but were judged to be clearly related to the study medication in <25% of patients. In a multicentre trial of 131 cancer patients over a period of up to 6 months, levels of efficacy and acceptability were better with tramadol (one 100mg SR tablet every 8–12 hours) than with buprenorphine (one sublingual 0.2mg tablet every 6–8 hours).[231] Adverse reactions were reported in 25% of patients taking tramadol and in 26% taking buprenorphine. Serious symptoms arose more fre-

Table VIII. Controlled trials of oral tramadol in chronic pain

Study	Type of pain	Study design	n	Duration	Analgesic drug	Dosage (mg/day)	Analgesic efficacy	Adverse events
Cancer pain								
Bono and Cullen[235]	Cancer	db, co	60	2 × 1wk	IR tramadol	300	T = B	T < B
					Buprenorphine	0.6		
Brema et al.[231]	Cancer	no	131	1–6mo	SR tramadol	200–300	T > B	T = B
					Buprenorphine	0.6–0.8		
Grond et al.[232]	Cancer	no	1659	1–967d	IR or SC tramadol	300–600	T = M	T < M
					IR morphine	10–60		
Osipova et al.[233]	Cancer	no	124	4–12wk	IR tramadol	368	T < M	T < M
					SR morphine	69–96		
Tawfik et al.[234]	Cancer	db	64	8wk	IR tramadol	217	T < M	T < M
					SR morphine	50		
Wilder-Smith et al.[236]	Cancer	db, co	20	2 × 4d	IR tramadol	375	T = M	T < M
					IR morphine	101		
Chronic pain								
Adler et al.[224]	Osteoarthritis	db,	279	1mo	SR tramadol	150–400	SR-T = IR-T	SR-T = IR-T
					IR tramadol	150–400		
Bird et al.[227]	Osteoarthritis	db, co	40	2 × 2wk	IR tramadol	200	T > PE	T < PE
					Pentazocine	150		
Gorali[234]	Chronic	db	84	1wk	IR tramadol	pm	T > T/N	NR
					Tilidine/naloxone	pm		
Jensen and Ginsberg[238]	Osteoarthritis	db	264	2wk	IR tramadol	300	T > D	T > D
					Dextropropoxyphene	300		
Pavelka et al.[240]	Osteoarthritis	db, co	60	2 × 4wk	IR tramadol	164	T = DI	T > DI
					Diclofenac	87		
Rauck et al.[241]	Chronic	db	380	4wk	IR tramadol	244	T = P/C	T = P/C
					Paracetamol/codeine	1407/140		
Roth[242]	Osteoarthritis	db	63	13d	IR tramadol + NSAID	250	T > PL	NR
					Placebo + NSAID			
Schnitzler et al.[243]	Low back	db	254	4wk	IR tramadol	200–400	T > PL	T > PL
					Placebo			
Silverfield et al.[244]	Osteoarthritis	db	368	10d	IR tramadol/paracetamol + NSAID	150–300/ 1300–2600	T/P > PL	T/P > PL
					Placebo + NSAID			
Sorge and Stadler[245]	Low back	db	205	3wk	SR tramadol	200	SR-T = IR-T	SR-T = IR-T

Continued next page

Table VIII. Contd

Study	Type of pain	Study design	n	Duration	Analgesic drug	Dosage (mg/day)	Analgesic efficacy	Adverse events
					IR tramadol	200		
Wilder-Smith et al.[240]	Osteoarthritis	db	60	1mo	SR tramadol	200	T > DC	T < DC
					SR dihydrocodeine	120		
Neuropathic pain								
Göbel and Stadler[241]	Postherpetic neuralgia	ra	35	6wk	IR tramadol	Up to 600	T = CL	T = CL
					Clomipramine	Up to 100		
Harati et al.[242]	Diabetic neuropathy	db	131	42d	IR tramadol	210	T > PL	T > PL
					Placebo			
Sindrup et al.[243]	Polyneuropathy	db, co	45	2 × 4wk	SR tramadol	200–400	T > PL	T > PL
					Placebo			

B = buprenorphine; C = codeine; CL = clomipramine; co = crossover; d = days; D = dextropropoxyphene; db = double-blind; DC = dihydrocodeine; DI = diclofenac; IR = immediate-release; M = morphine; mo = months; N = naloxone; no = nonrandomised open; NR = not reported; P = paracetamol; PE = pentazocine; PL = placebo; prn = as needed; ra = randomised; SC = subcutaneous; SR = sustained-release; T = tramadol; Til = tilidine; wk = weeks; > indicates superior to; = indicates equivalent to; < indicates inferior to.

quently in the buprenorphine group (19% vs 10%).

4.2 Chronic Non-Cancer Pain

Several studies have demonstrated the effectiveness of oral tramadol in the treatment of chronic pain of nonmalignant origin (table VIII). In a double-blind study involving 264 osteoarthritis patients, oral treatment with tramadol 300mg was compared with oral dextropropoxyphene 300mg.[239] Pain relief was superior with tramadol; at the end of the second week, 72% of tramadol-treated patients and 53% of dextropropoxyphene-treated patients had symptom improvement during daily activities. Tramadol was associated with a higher incidence of adverse effects, especially nausea, dizziness and vomiting, which led to more withdrawals from the study. However, in view of reports of fatal overdoses with dextropropoxyphene,[254] the authors concluded that tramadol should be preferred for chronic pain.

Bird et al.[237] found lower pain scores and less morning stiffness in 40 patients with osteoarthritis who received tramadol 200mg compared with those treated with pentazocine 150mg in a double-blind crossover study (2 × 2 weeks). Adverse events were reported by 53% of patients taking tramadol and 78% of those taking pentazocine. Patients rated overall efficacy higher for tramadol than for pentazocine.

The analgesic efficacy of oral tramadol drops was superior to that of tilidine/naloxone drops in a double-blind study in patients with various chronic pain conditions.[238] Unfortunately, pain aetiology was not mentioned in this report.

Another double-blind crossover study (2 × 4 weeks) compared diclofenac and tramadol in 60 patients with painful osteoarthritis.[240] The dosage of tramadol (50–100mg up to three times daily) and diclofenac (25–50mg up to three times daily) could be individually titrated by the patients. Both tramadol (mean dosage 164 mg/day) and diclofenac (mean dosage 87 mg/day) improved pain intensity and functional parameters, and there was no difference between the groups. More patients reported adverse events with tramadol than with diclofenac (20% vs 3%).

In a 4-week, double-blind study, tramadol was compared with a combination of paracetamol and codeine in 390 patients >65 years of age who had a variety of malignant and nonmalignant pain conditions.[241] Patients were allowed to titrate the dosage according to pain intensity. There was a tendency for better pain relief with tramadol (mean dosage 244 mg/day) than with paracetamol/codeine (mean dosage 1407/140 mg/day), but the difference was not significant. Nausea, constipation, dizziness and somnolence were the most common adverse events, with no differences between the groups.

In a study of patients with chronic low back pain, 380 subjects were treated with tramadol up to 400 mg/day.[243] Of these, 254 entered a double-blind study with tramadol 200–400 mg/day or placebo. The discontinuation rate because of therapeutic failure was 21% in the tramadol group and 51% in the placebo group. There were better scores on the visual analogue pain scale, the McGill Pain Questionnaire and the Roland Disability Questionnaire among tramadol patients compared with placebo patients.

Roth[242] investigated the efficacy of tramadol in 63 osteoarthritis patients who experienced breakthrough pain while taking a NSAID. In addition to their stable daily NSAID regimen, patients were randomised to a 13-day double-blind phase of adjunctive therapy with tramadol 50–100mg every 4–6 hours as needed, or placebo. The time to exit from the study because of insufficient pain relief tended to be longer in the tramadol group. Patients' overall assessment and investigator's rating of global improvement were significantly better with tramadol.

In 308 patients with osteoarthritis achieving inadequate pain relief from traditional NSAIDs or cyclooxygenase (COX)-2-selective inhibitors, the addition of tramadol/paracetamol tablets to existing therapy was investigated in a double-blind placebo-controlled study.[244] Supplementation with one or two tramadol/paracetamol (37.5/325mg) tablets four times daily was superior to placebo on the patients' and physicians' overall assessments.

Two studies demonstrated that a slower titration rate of tramadol can improve its tolerability in patients who previously discontinued therapy because of nausea and/or vomiting.[255,256]

4.2.1 Sustained-Release

In experimental pain, SR tramadol was effective for 12 hours and produced fewer adverse effects than the standard formulation, presumably because high peak concentrations did not occur.[36,61] An open, noncomparative study investigated the efficacy of SR tramadol in 1893 patients with chronic pain.[257] Daily dosages of between 1 × 100mg and 3 × 100mg were administered for a period of 4 weeks. Efficacy was assessed as very good by 46% of patients and good by 42% of patients.

A randomised, double-blind study compared the analgesic efficacy and tolerability of tramadol SR tablets and IR capsules in patients with chronic low back pain, of whom 103 received tramadol SR (2 × 100 mg/day) and 102 received tramadol IR (4 × 50 mg/day) over 3 weeks.[245] There was no difference in pain relief between tramadol SR and IR (59% vs 59% of patients with sufficient pain relief). Adverse events were reported at a similar rate in both groups (54% vs 53%). These results confirmed the equivalence with regard to efficacy and tolerability of twice daily administration of tramadol SR compared with four-times-daily administration of tramadol IR. Another study compared SR tablets once daily (1 × 150–400 mg/day) with IR capsules (3 × 50mg up to 4 × 100 mg/day) in 279 patients with osteoarthritis.[236] There was no difference between treatments and both produced good pain control and a similar adverse event profile; 49% of SR tramadol recipients and 52% of IR tramadol recipients withdrew, mostly because of adverse events.

Wilder-Smith et al.[246] compared analgesia and adverse effects of tramadol (2 × 100 mg/day) and dihydrocodeine (2 × 60 mg/day), both in long-acting formulations, in 60 osteoarthritis patients with strong pain refractory to treatment with NSAIDs. During the treatment period of 1 month, the dihydrocodeine dosage was increased to 180 mg/day in five patients and the tramadol dosage to 300 mg/day in two patients. The pain intensity at rest, but not during movement, was significantly lower with tramadol. The frequency of defecation was lower and stools were harder with dihydrocodeine.

4.3 Neuropathic Pain

For a long time, neuropathic pain has been considered to be unresponsive to opioids. Most authors

now agree that opioids may be effective on such pain provided that sufficient dosages are achieved [258,259] The monoaminergic effect of tramadol, although substantially weaker, is similar to that of the tricyclic antidepressants commonly used in neuropathic pain. Therefore, tramadol is an interesting alternative to strong opioids in the treatment of neuropathic pain. The antinociceptive efficacy of tramadol was demonstrated in experimental models of neuropathic pain.[260,261] Several clinical studies have demonstrated the analgesic efficacy of tramadol in neuropathic pain, but more controlled trials are required. In postmarketing surveillance of SR tramadol, 485 of 7710 documented patients had only neuropathic pain [262] Patients were treated over a period of 4 weeks with a mean tramadol dosage of 205 mg/day; 83% reported excellent or good, 12% adequate and 5% inadequate pain relief

In an open study, 35 patients with postherpetic neuralgia were randomised to oral tramadol up to 600 mg/day or clomipramine up to 100 mg/day with or without levomepromazine 100 mg/day [247] Ten patients on tramadol and 11 patients on clomipramine completed the 6-week treatment phase Nine of ten patients in the tramadol group and six of 11 patients in the clomipramine group rated their analgesia as excellent, good or satisfactory The incidence of adverse events was similar in both groups (77% vs 83%).

A total of 131 patients with painful diabetic neuropathy were treated with oral tramadol or placebo in a randomised, double-blind study over 42 days [248] Tramadol, at an average dosage of 210 mg/day, was significantly more effective, whereas nausea, constipation and headache were reported more frequently. Patients in the tramadol group scored significantly better in physical and social functioning ratings than patients in the placebo group. A total of 117 patients (56 former tramadol and 61 former placebo) entered an open-label extension of up to 6 months and received tramadol 50–400 mg/day.[263] Mean pain relief scores (2 4 vs 2 2) were similar after 30 days in the former placebo and former tramadol groups, respectively, and were maintained for the duration of the study Four patients discontinued therapy because of ineffective pain relief; 13 patients discontinued because of adverse events

A randomised, double-blind, placebo-controlled, crossover study investigated tramadol in painful polyneuropathy during two treatment periods of 4 weeks' duration [249] After baseline observations, 45 patients were assigned to tramadol SR tablets (200 mg/day titrated up to 400 mg/day) or placebo. Thirty-four patients completed the study. Their ratings for pain (median 4 vs 6), paraesthesia (4 vs 6) and touch-evoked pain (3 vs 5) were lower on tramadol than on placebo. Tramadol was associated with a higher rate of adverse events (82% vs 35%) The investigators concluded that tramadol appears to relieve both ongoing pain symptoms and the key neuropathic pain feature allodynia in polyneuropathy

The above studies demonstrate that tramadol can relieve neuropathic pain. Further crossover studies would be useful to compare the efficacy of tramadol with that of other opioids in different types of neuropathic pain. Of most importance are long-term studies demonstrating effectiveness and tolerability of tramadol over several months compared with anticonvulsants, antidepressants or antiarrhythmics.

4.4 Place of Tramadol in Chronic Pain

Many patients with chronic pain are inadequately treated and suffer needlessly. Opioids are often withheld because of irrational fears of respiratory depression, dizziness, confusion, addiction and tolerance However, adequate use of opioids according to the guidelines of the WHO has been shown to be an efficacious, well tolerated and simple method for cancer pain relief until death.[264] Because of these good results, opioids are indicated not only in most patients with cancer pain, but also in a subgroup of patients with chronic pain of nonmalignant origin

The regular administration of oral analgesics is the mainstay of cancer pain treatment.[265] Depending on pain intensity, analgesics are selected 'by the ladder', switching from non-opioids (WHO step 1) to weak opioids (step 2) and then to strong opioids (step 3) Analgesics are combined with co-analgesics (e g. antidepressants, anticonvulsants, corticosteroids) to treat special pain conditions, or with adjuvants (e g. antiemetics, laxatives) against other symptoms The effectiveness and feasibility of the WHO guidelines have been demonstrated in several clinical studies.[266,267]

The distinction between weak and strong opioids, made by the WHO for practical purposes, is arbitrary and does not reflect pharmacological differences. In contrast with strong opioids, the weak opioids listed in the WHO guidelines[265] (codeine, dihydrocodeine, dextropropoxyphene, standardised opium and tramadol) have a maximum recommended dosage and are not scheduled in many countries. The maximum dosages were chosen from experience that higher dosages are associated with progressively more adverse effects, notably nausea and vomiting, that outweigh any extra analgesic effect, but have not been formally determined in clinical studies.

Due to lack of alternatives in many countries, codeine was regarded as the standard drug among the weak opioids. Codeine is a prodrug of morphine and has, therefore, the same efficacy and adverse effect profile as low doses of morphine. For this reason, there have been continuous demands to abolish WHO step 2 and to initiate early therapy with low doses of morphine.[268] However, the three-step analgesic ladder of the WHO has an important political and educational impact and should not be altered.[269]

Tramadol can be recommended as a well tolerated and efficacious drug for step 2 of the WHO guidelines for cancer pain management. Compared with morphine, tramadol is more freely available and offers pain relief to many patients who would otherwise receive no opioids at all or at a later time. Furthermore, several comparative trials suggest that tramadol has a better adverse effect profile than other opioids, although long-term studies comparing equianalgesic dosages of tramadol and other opioids are required for confirmation. The incidence of nausea can be reduced by antiemetics or careful dosage titration. If cancer pain cannot be controlled by adequate dosages of tramadol, morphine or other strong opioids are required.

The oral administration of SR formulations has the advantage of continuous pain relief and better compliance. In many cancer patients, the combination of tramadol with non-opioid analgesics and adjuvants can improve efficacy and safety. When oral administration is not longer possible, tramadol can be given subcutaneously.

Tramadol, particularly the SR formulation, may also be used for long-term treatment of chronic pain of nonmalignant origin, either alone or in combination with non-opioid analgesics. Many studies have demonstrated its effectiveness in pain from osteoarthritis. Special advantages are expected in neuropathic pain.

5. Tolerability

Safety data for tramadol have recently been summarised by Cossmann et al.[270] They considered information from phase II to IV clinical studies and postmarketing surveillance studies, covering safety data from a total of more than 21 000 patients. The most frequent adverse events were nausea (6.1%), dizziness (4.6%), drowsiness (2.4%), tiredness/fatigue (2.3%), sweating (1.9%), vomiting (1.7%) and dry mouth (1.6%). Adverse events that occurred in <1% but >0.1% of patients were somnolence, hypotension, flush, stomach upset, constipation, nausea plus vomiting, sedation, circulatory failure, sleep disorder, pruritus, abdominal pain, diarrhoea, tachycardia and local irritation. Other events occurring in <0.1% of patients were not shown, because more than 150 descriptive terms were involved.[270]

The profile for single-dose or short-term (<24 hours) administration (6011 patients) is quite similar, qualitatively and quantitatively, to that for long-term administration (15 211 patients), as shown in figure 1.[270]

The incidence of most adverse events, in particularly nausea, was higher in controlled trials than in postmarketing surveillance studies (table IX). This is not unexpected, because controlled studies are performed under more stringent conditions.[270] In addition, most controlled studies involved postoperative use and had been carried out in hospitals, whereas the postmarketing surveillance studies were all in outpatients.[270] The incidence of adverse events depends also on the mode of administration (table IX). Following parenteral administration, relatively high initial plasma concentrations are attained, particularly when an injection is administered too rapidly.

Qualitatively, the profile of adverse effects of tramadol corresponds to that known for opioids,

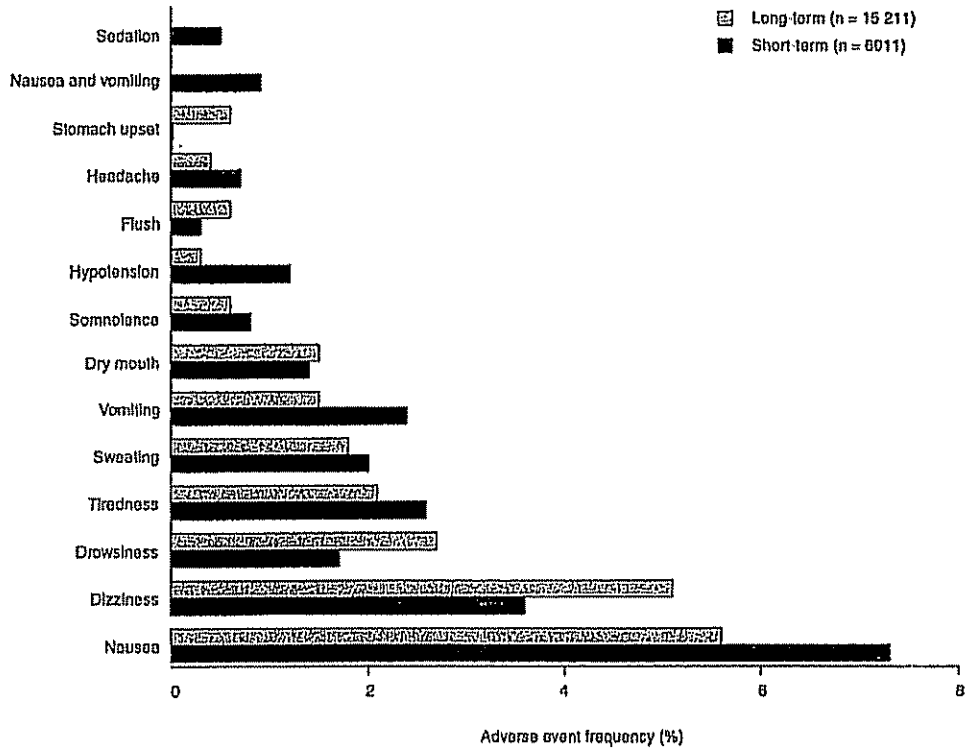

Fig. 1. Frequency of adverse events in clinical trials and postmarketing surveillance studies of tramadol (reproduced from Cossmann et al,[270] with permission)

although there are some essential differences. Several long-term trials have shown that the rate of constipation[232-235] and nausea [233-235] was lower for tramadol than for morphine. In postoperative pain, some studies found that tramadol is associated with an increased risk of nausea and vomiting,[118,125,147,179,181] whereas others reported no difference between tramadol and other opioids.[114,116,124,127,132,160] Of particular significance, tramadol had less respiratory depressant potential than morphine,[25,131,141,179-182] buprenorphine,[97,130] oxycodone,[228] pethidine[98,191] and nalbuphine.[271] The use of tramadol in postoperative pain, however, is not completely free from problems, as two case reports describe respiratory depression.[272,273] A patient with undiagnosed hyperthyroidism developed respiratory depression after an infusion of tramadol 600mg following abdominal surgery.[273] He recovered completely after repeated doses of naloxone. Although faster metabolism could be expected in hyperthyroid patients, no explanation is available for this mishap. Another patient with impaired renal function became respiratory insufficient during treatment with tramadol 400 mg/day.[272] He also recovered completely following naloxone infusion. A few cases of respiratory depression have been reported to the spontaneous reporting system of Grünenthal GmbH.[270] In the cases where the cause could be attributed to tramadol, mainly high parenteral doses of up to 1000mg had been administered, or the patients had considerably compromised function.

Table IX. Incidence of adverse events with tramadol observed in controlled trials and postmarketing surveillance studies classified by route of administration (reproduced from Cossmann et al,[270] with permission)

Adverse event	Patients experiencing event (%)						
	short-term administration					long-term administration	
	PO (n = 352)	IM (n = 548)	IV (n = 759)	PCA (n = 140)	PMS[a] (n = 3536)	PO (n = 799)	PMS[b] (n = 13 129)
Nausea	3.1	17.8	16.2	20.7	4.2	21.4	4.8
Dizziness	1.7	2.9	3.2	6.4	4.4	18.7	4.6
Drowsiness	0.3	10.3	3.6			8.5	1.1
Tiredness	5.7	3.3	6.9		1.9	5.9	2.1
Sweating	1.1	4.6	3.6	15.0	0.8	7.9	0.8
Vomiting	2.8	7.0	6.2	11.4	0.5	9.8	1.0
Dry mouth	3.1	1.3	2.8	14.3	0.7	4.3	1.5

a Parenteral

b Oral or parenteral

IM = intramuscular; IV = intravenous; PCA = patient-controlled analgesia; PMS = postmarketing surveillance; PO = oral.

In their review, Cossmann et al [270] presented data from the spontaneous reporting system reflecting the time period 1977–93, in which more than one billion single dose units were distributed. The most frequently documented adverse effects in formal studies, namely nausea, vomiting, dizziness, drowsiness, tiredness, sweating and dry mouth, were noted infrequently in spontaneous reports, since these adverse effects are usually recognised as typical of opioids and described in the product information.[270] There have been some spontaneous reports of allergic and anaphylactic reactions, but the incidence was lower than 0.1%, corresponding to the generally accepted knowledge that the incidence of these reactions is low with opioids. Most of the reports dealt with psychiatric disorders, mainly dependence and abuse, and central and peripheral nervous system disorder, mainly seizures.

In a cohort of 9218 adult tramadol users, fewer than 1% had a presumed incident seizure.[274] Risk was highest among those aged 25–54 years, those with more than four tramadol prescriptions, and those with history of alcohol abuse, stroke, or head injury. A case-control study among users was conducted to validate incident seizure outcomes from medical records.[274] Only eight cases were confirmed and all had cofactors associated with increased seizure risk. Experimental data from rats confirm that a pre-existing lowered seizure threshold increases the risk of tramadol-induced seizures.[275] An evaluation of a General Practice Research Database identified 21 cases of idiopathic seizures in 11 383 subjects.[276] Three patients were exposed to tramadol, ten to other opioids, three to both tramadol and other opioids, one to other analgesics, and four to no analgesics. The risk of idiopathic seizures was similarly elevated in each analgesic exposure category compared with non-users, suggesting that the risk for patients taking tramadol was not increased compared with other analgesics.[276]

Tramadol has a low abuse potential and is not classified as a controlled drug. Epidemiological data collected in Germany over 14 years through the substance abuse warning system indicates that tramadol abuse is less common than abuse of dihydrocodeine or codeine, despite much greater use of tramadol.[3] Most of the patients were abusing other drugs or alcohol at the same time as abusing tramadol.[3] After approval of tramadol as a non-scheduled drug in 1995, a postmarketing surveillance programme was started in the US.[277] The data for 3 years show that the reported rate of abuse has been low. Although a period of experimentation seemed to occur in the first 18 months after its introduction, which reached a peak rate of approximately two cases per 100 000 patients exposed, the reported rate of abuse has significantly declined, reaching levels of less than one case per 100 000 patients in the second 18 months. The overwhelming majority of abuse cases (97%) have been found

to occur among individuals with a history of substance abuse [277]

Further evidence for the low abuse potential of tramadol comes from a double-blind placebo controlled study in volunteers who were previous addicts.[278] Morphine 15 and 30mg produced typical subjective effects, opioid identification and miosis. Tramadol 75 and 150mg was not different from placebo. Although tramadol 300mg was identified as an opioid, it produced no other morphine-like effects and was not liked. These observations were confirmed in a study involving volunteers enrolled in a methadone maintenance programme.[279] Tramadol 100 and 300mg neither produced morphine-like effects nor precipitated a withdrawal syndrome; its subjective, behavioural and physiological effects were not different from those of placebo.

Overdose of tramadol is associated with neurological toxicity; cardiovascular toxicity has not been reported [280] Prospective data from seven poisons centres in the US indicate that the most common symptoms of tramadol overdose are lethargy (30%), nausea (14%), tachycardia (13%), agitation (10%), seizures (8%), coma (5%), hypertension (5%) and respiratory depression (2%). In case reports describing tramadol toxicity, most patients received concomitant medications or alcohol.[281-285]

6. Conclusions

Tramadol offers an important alternative to other opioids, because the complementary and synergistic actions of the two enantiomers (opioid and reuptake inhibitor of norepinephrine and serotonin) enhance its analgesic effects and improve its tolerability profile. The analgesic efficacy of tramadol has been demonstrated in different acute and chronic pain syndromes, being comparable with that of various other opioid and non-opioid analgesics. Unlike other opioids, tramadol has no clinically relevant effects on respiration, is associated with a low incidence of constipation, shows positive effects on immune system function and has a low potential for abuse and dependence. In addition, tramadol is not scheduled in most countries. It is a further advantage of tramadol that the best mode of administration can be selected for the individual patient and the specific situation, because drops, capsules and SR preparations for oral administration, suppositories and formulations for intramuscular, intravenous and subcutaneous injection are available. Tramadol has proved to be an effective and well tolerated analgesic in the treatment of acute and chronic pain.

Tramadol can be recommended as a basic analgesic for the treatment of moderate-to-severe acute pain. The most frequent adverse event is nausea. Tramadol is particularly useful in patients with poor cardiopulmonary function, including the elderly, the obese, smokers, and after surgery of the thorax or upper abdomen, in situations with an increased risk of respiratory depression, including labour pain, paediatric surgery, day-case surgery and general wards without close supervision, in patients in whom non-opioid analgesics need to be used with caution and in patients with compromised immunity or cancer.

Tramadol can be recommended as an opioid for step 2 of the WHO guidelines for cancer pain treatment. Because IR preparations should be administered every 4 (up to 6) hours, SR preparations that can be administered every 8–12 hours are preferred. Tramadol can be combined with non-opioid analgesics or adjuvants. If tramadol at dosages up to 600 mg/day is not adequate, morphine or other opioids of step 3 are required. Tramadol can also be recommended in the treatment of chronic pain of nonmalignant origin, such as osteoarthritis or neuropathic pain. Further crossover studies would be useful to compare the efficacy of tramadol with that of other opioids in different types of chronic pain. Of most importance are long-term studies aiming to demonstrate the effectiveness and tolerability of tramadol over several months.

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EXHIBIT E

Serum concentrations of tramadol enantiomers during patient-controlled analgesia

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Aims Tramadol, a centrally acting analgesic, is used as a racemate containing 50% of a (+)- and 50% of a (−)-enantiomer. This paper presents the pharmacokinetic results of postoperative patient-controlled analgesia using (+)-tramadol, (−)-tramadol or the racemate.

Methods Ninety-eight patients recovering from major gynaecological surgery were treated in a randomised, double-blind study with (+)-tramadol, (−)-tramadol or the racemate. Following an i.v. bolus up to a maximum of 200 mg, patient-controlled analgesia with demand doses of 20 mg was made available for 24 h. Prior to each demand, the serum concentrations of the enantiomers of tramadol and its metabolite M1 were measured in 92 patients.

Results The mean concentrations of tramadol during the postsurgery phase were 470 ± 323 ng ml^{-1}, 590 ± 410 ng ml^{-1} and 771 ± 451 ng ml^{-1} in the (+)-, racemate- and (−)-group, respectively ((+) *vs* (−), $P<0.05$); the mean concentrations of the metabolite M1 were 57 ± 18 ng ml^{-1}, 84 ± 34 ng ml^{-1} and 96 ± 41 ng ml^{-1} in the (+)-, racemate- and (−)-group, respectively ((+) *vs* (−) and (+) *vs* racemate, $P<0.05$). The mean concentrations of (+)-tramadol and (+)-M1 were lower in the racemate- than in the (+)-group ($P<0.05$), those of (−)-tramadol and (−)-M1 were lower in the racemate than in the (−)-group ($P<0.05$). In the racemate group, the mean serum concentrations of (+)-tramadol were higher than those of (−)-tramadol ($P<0.05$), whereas the mean serum concentrations of (−)-M1 were higher than those of (+)-M1 ($P<0.05$).

Conclusions The therapeutic serum concentration of tramadol and M1 showed a great variability. The lowest mean concentrations were measured in the (+)-group and the highest in (−)-group. This is in agreement with the clinical finding that (+)-tramadol is a more potent analgesic than (−)-tramadol.

Keywords: enantiomer, opioid, pharmacokinetic, postoperative pain, tramadol

Introduction

Tramadol hydrochloride (1RS,2RS)-2-[(dimethylamino)-methyl]-1-(3-methoxyphenyl)-cyclohexanol hydrochloride, is a clinically effective, centrally acting opioid analgesic [1, 2]. It is structurally similar to morphine in containing an aromatic ring system with three carbon atoms spaced away from a basic nitrogen centre. Tramadol displays a low affinity for opioid receptors with a marginal preference for μ-receptors [1, 2]. The analgesic effect is also mediated by the inhibition of neuronal reuptake of noradrenaline and serotonin [3].

The marketed product is a racemate mixture ((±)-T) containing 50% of a (+)-enantiomer ((+)-T) and 50% of a (−)-enantiomer ((−)-T). *In vitro* (+)-T exerts opioid effects and inhibits serotonin re-uptake, whereas (−)-T is a noradrenaline re-uptake inhibitor [4]. In animal models, both enantiomers revealed antinociceptive effects, with (+)-T being the more potent [4].

Tramadol undergoes biotransformation in the liver and is excreted via the kidneys. Of 11 known metabolites, only the *O*-demethyl-tramadol (M1) is pharmacologically active [5]. M1 has a remarkably greater affinity for the μ-receptors than tramadol, but plays no dominant role in tramadol-induced analgesia, because M1 has difficulties to penetrate the blood–brain barrier [6].

In a phase II pilot study using i.v. patient-controlled analgesia (PCA), (+)-T and (±)-T were more potent analgesics than (−)-T, whereas the incidence of adverse events was higher in (+)-T patients than in (±)-T

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patients [7] It was concluded from the clinical results that the racemate is superior to either enantiomer alone, taking into account both efficacy and safety aspects The pharmacokinetic results of this investigation are reported in the present paper

The aim of the present study was to determine the therapeutic serum concentrations of the enantiomers of tramadol and its metabolite M1 during treatment of postoperative pain with tramadol racemate or either enantiomer alone

Methods

Demographic data and design of this randomised, double-blind study have been published in detail [7] After Institutional Ethics Committee approval, patients gave written informed consent The study included 99 female patients after vaginal hysterectomy or gynaecological laparotomy during opioid-free anaesthesia Patients suffering from severe pain were randomly allocated to treatment with either (+)-T, (±)-T or (−)-T, which were obtained from Grünenthal GmbH (Stolberg, Germany) Initially, an intravenous bolus injection (50 mg up to a maximum of 200 mg) was performed, until acceptable pain relief was obtained This was followed by single on-demand boluses of 20 mg of the respective study medication through a PCA system (lockout time: 5 min)

Blood sampling

For determination of the therapeutic serum concentrations, 3 ml blood samples were taken prior to each on-demand application via the PCA system (maximal 50 ml per patient). Blood was sampled via an indwelling cannula, which was not used to apply the study medication After complete coagulation (about 20 min) the blood samples were centrifuged for 10 min at 2800 *g* and the serum was stored at −20° C until analysis

Analytical methods

The concentrations of (+)-T and (−)-T in serum were determined by a modified gas chromatographic-mass spectrometric method on a column coated with CP-Cyclodextrin–2,3,6-m-19 [8, 9] The method involves the use of [$^{2}H_{2}$, ^{15}N]-tramadol hydrochloride as internal standard and chemical ionization with isobutane employing single-ion monitoring for quantification

The (+)-M1 and (−)-M1 serum concentrations were determined after derivatization with diazoethane by gas chromatography on a column coated with CP-Cyclodextrin-β-2,3,6-m-19 and with a nitrogen-selective (NDP) detector [10]

The serum samples of this study were analytically determined in 15 series of (+)-T and (−)-T and 21 series of (+)-M1 and (−)-M1 determinations Each series also contained eight calibration samples (5–250 ng 0 5 ml^{-1}) and four control samples (5, 20, 40 and 100 ng 0 5 ml^{-1}) If more than two concentrations of the control samples were outside ± 15% of the nominal concentration, the results were rejected and the series was repeated

The lower limit of quantification was 5 ng ml^{-1} Calibration curves were linear and showed only small differences (0–8%) between nominal and recalculated calibration values The mean accuracy was 5 8 ± 5 6% for (+)-T, 2 4 ± 1 7% for (−)-T, 4 5 ± 1 2% for (+)-M1 and 4 6 ± 4 0% for (−)-M1 The mean precision (%CV) was 7 4 ± 6 6% for (+)-T, 7 1 ± 6 0% for (−)-T, 8 7 ± 6 8% for (+)-M1 and 11 4 ± 6 5% for (−)-M1

Statistics

Inter-individual means and standard deviations (s d) were calculated for statistical analysis Analysis of variance including Scheffe's test for pair-wise comparison was used to compare the concentrations between the three treatment groups, the unpaired *t*-test to compare the concentrations of the (+)-enantiomers between the (+)- and (±)- group and of the (−)-enantiomers between the (−)- and the (±)- group and the paired *t*-test to compare the concentrations of the two enantiomers in the racemate group (SPSS, $P<0\ 05$)

Results

Ninety-eight patients received study medication One of the patients allocated to the (−)-group did not receive drug due to respiratory depression The clinical results have been published in detail [7]. The duration of PCA using (+)-T, (±)-T and (−)-T was 20, 21 and 12 h, respectively Patients of the (+)-, (±)- and (−)-group received 289 mg, 316 mg and 356 mg of the respective study medication Twenty-seven patients treated with (+)-T, 25 with (±)-T and 13 with (−)-T were satisfied with pain relief (responders) Nausea and vomiting were the most frequently observed events, with highest occurrence in (+)-T patients

One patient of the (+)-group and five of the (±)-group were excluded from the statistical evaluation of the serum concentrations, because no demand-boluses were administered or no blood was sampled prior to the boluses. Means of 6 ± 3, 7 ± 3 and 7 ± 4 concentrations per individual were calculated in the patients of the (+)-, (±)- and (−)-group, respectively

The mean concentrations of tramadol were 470 ng ml^{-1}, 590 ng ml^{-1} and 771 ng ml^{-1} (Table 1)

Treatment group	Patients n	Serum concentration (ng ml^{-1}) (+)-T	T_{sum}	(−)-T
(+)	32	470±323	—	—
Racemate	28	307±211[a]	590±410	282±198[b]
(−)	32	—	—	771±451[a,c]

Table 1 Therapeutic serum concentrations (mean±s.d.) of tramadol racemate and enantiomers

T_{sum} = sum of (+)- and (−)-T
[a]Difference from (+)-T in the (+)-group statistically significant, $P<0.05$; [b]Difference from (+)-T in the racemate group statistically significant $P<0.05$; [c]Difference from (−)-T in the racemate group statistically significant $P<0.05$

and those of M1 were 57 ng ml^{-1}, 84 ng ml^{-1} and 96 ng ml^{-1} (Table 2) in the (+)-, (±)- and (−)-group, respectively. The mean concentrations of (+)-T and (+)-M1 were lower in the (±)- than in the (+)-group, those of (−)-T and (−)-M1 were lower in the (±)- than in the (−)-group. In the (±)-group, the mean serum concentrations of (+)-T were higher than those of (−)-T, whereas the mean serum concentrations of (−)-M1 were higher than those of (+)-M1.

Discussion

The venous blood samples were taken immediately before a patient's self-controlled administration, i.e. at a point in time at which the patient was just becoming dissatisfied with analgesia. Previously, these concentrations were described as 'minimal effective concentrations' [11–13]. However, because no quantitative data of the part of (+)-T, (−)-T, (+)-M1 and (−)-M1 in the analgesic effect of tramadol are available, the measured concentrations cannot be defined as 'minimal effective'. In addition, this study demonstrated a great inter and intra-individual variability in postoperative serum concentrations and could not fix narrow analgesic threshold concentrations. Therefore, the term 'therapeutic concentrations' was preferred.

The pharmacokinetic results can explain the clinical findings, that (+)-T is a more potent analgesic than (−)-T but is associated with a higher incidence of opioid related side-effects than (−)-T and the racemate. This is consistent with the clinical suggestion that the racemate is superior to either enantiomer alone in the treatment of severe postoperative pain.

The mean therapeutic serum concentrations of tramadol and M1 in the (+)-group were statistically significantly lower than those in the (−)-group. This finding confirms, that (+)-T is a more potent analgesic than (−)-T. The mean concentrations in the racemate group (sum of (+)-T and (−)-T; sum of (+)-M1 and (−)-M1) were between those in the (+)- and the (−)-group; of these differences, only that for M1 between the (+)- and the racemate group was statistically significant. This is consistent with the clinical suggestion, that the racemate is only slightly less potent than (+)-T, but cannot confirm, that the racemate is markedly more potent than (−)-T.

The mean concentrations of the (+)-enantiomers of tramadol and M1, which are responsible for opioid effects, were significantly lower in the racemate group than in the (+)-group. This finding can explain that the incidence of opioid related adverse events (nausea) was lower in the racemate group than in the (+)-group.

On the assumption that the enantiomers have a similar volume of distribution, (−)-T is metabolized slightly faster to (−)-M1 than (+)-T to (+)-M1. In the racemate group, the mean serum concentrations of (+)-T were higher than those of (−)-T, whereas the mean serum concentrations of (−)-M1 were higher than those of (+)-M1.

The mean tramadol concentration in the racemate group (590 ng ml^{-1}) was markedly higher than that in a previous investigation (298 ng ml^{-1}) of tramadol race-

Treatment group	Patients n	Serum concentration (ng ml^{-1}) (+)-M1	$M1_{sum}$	(−)-M1
(+)	27	57±18	—	—
Racemate	22	33±15[a]	84±34[a]	51±21[b]
(−)	32	—	—	96±41[a,c]

Table 2 Therapeutic serum concentrations (mean±s.d.) of M1 racemate and enantiomers

$M1_{sum}$ = sum of (+)- and (−)-M1
[a]Difference from (+)-M1 in the (+)-group statistically significant, $P<0.05$; [b]Difference from (+)-M1 in the racemate group statistically significant $P<0.05$; [c]Difference from (−)-M1 in the racemate group statistically significant, $P<0.05$

mate using an identical study design [13]. This can be explained by the higher tramadol consumption in the present study (316 mg *vs* 258 mg) and the fact, that the present patients received no opioids whatsoever during anaesthesia, whereas the other patients received at least 5 $\mu g\,kg^{-1}$ fentanyl intraoperatively. A higher concentration of tramadol racemate (median: 916 $ng\,ml^{-1}$) was measured by Hackl *et al* [12] combining the PCA with a continuous infusion (12 mg h^{-1}) independent of the demands. Previous data regarding serum concentrations of the (+)-T, (−)-T, (+)-M1, or (−)-M1 are not available, since the present study describes the first administration of the enantiomers to humans.

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